

EVALUATION OF THE BINDING PROPERTIES OF ENZYME - HYDROLYZED
CASSAVA STARCH IN CHLOROQUINE PHOSPHATE TABLET FORMULATIONS

BY

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DECLARATION

I declare that the work in this thesis titled "Evaluation of the binding properties of Enzyme -hydrolyzed cassava starch in chloroquine phosphate 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. P.G. Bhatia.

The information derived from the literature has been duly acknowledged in the text and a list of references has been provided. No part of this thesis was ever presented for another degree or diploma at this or any other institution.

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CERTIFICATION

This thesis titled “EVALUATION OF THE BINDING PROPERTIES OF ENZYME - HYDROLYSED STARCH IN CHLOROQUINE PHOSPHATE TABLET FORMULATION” by Ganiyat Toyin ABDULSALAM meets the regulations governing the award of the degree of Master of Science in 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 Almighty Allah (S.W.T), my dear Mother, loving husband, kids, siblings and to the memory of my late father Abdul Fatah Abdulsalam, may Allah have mercy on his soul (amin).

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ABSTRACT

Starch is a major carbohydrate, easily extractable from various sources like cassava, maize, potato etc which find wide application in various food and Pharmaceutical industries. There has been a lot of attempt to modify this highly flexible polymer with the aim of extending and enhancing its applications.

Native cassava starch (NCS) was extracted from the tubers of freshly harvested cassava. Enzyme- hydrolysed starch (EHS) was produced from Native cassava starch (NCS) using enzymatic hydrolysis method with α – amylase as the enzyme.

The physicochemical characterization for NCS and EHS was conducted using standard methods, such as flow rate, angle of repose, mean particle size, moisture content, Carr's index, Hausner's ratio, ash content, swelling power, pH, bulk and tapped densities.

Chloroquine tablets were formulated by wet granulation method and direct compression using EHS, MCC, MS and NCS as binders at different concentrations of 2.5, 5, 7.5 and 10 %w/v. The tablet characteristics were evaluated and compared with that of MCC and maize starch.

The mechanical properties using crushing strength and friability for NCS and EHS were carried out. The crushing strength increased with increase in binder concentration while friability decreased. The disintegration time also increased with increase in binder concentration. The disintegration and dissolution profile of the tablets were studied and these were much faster for EHS tablets when compared to that of PVP.

Using the direct compression method, crushing strength was found to increase with increase in binary mixture of MCC and the friability increases with increase in the

proportion of EHS. The Disintegration time was above 60 min., the tablet continued to swell, absorbing more water without disintegrating for the period of the study.

The study found out that EHS is comparable to standard starches and can be used as a binder in wet granulation and direct compression method in Pharmaceutical industries to produce the tablets.

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List of Abbreviations, Definitions, Glossaries and Symbols

a	Minimum porosity
API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
C.I	Carr's Index
d	Diameter of tablet
E	Porosity
EHS	Enzyme - Hydrolyzed starch
KgF	Kilogram force
M.S.	Maize starch
MCC	Microcrystalline Cellulose
NCS	Native Cassava Starch
P	Applied Pressure/Load
Ps	particle density
PVP	Polyvinyl pyrrolidone
T	thickness of tablets
Ts	Tensile Strength
USP	United States Pharmacopoeia
W	Weight of tablet

KEYS;

A ₁	-	Native Cassava starch at binder conc. 2.5%
A ₂	-	Native Cassava Starch (5%)
A ₃	-	Native Cassava Starch (7.5%)
A ₄	-	Native Cassava Starch (10%)
B ₁	-	Enzyme-hydrolyzed Starch (2.5%)
B ₂	-	Enzyme-hydrolyzed Starch (5%)
B ₃	-	Enzyme-hydrolyzed Starch (7.5%)
B ₄	-	Enzyme-hydrolyzed Starch (10%)
C ₁	-	Maize starch BP (2.5%)
C ₂	-	Maize starch (5%)
C ₃	-	Maize starch (7.5%)
C ₄	-	Maize starch (10%)
D ₁	-	Polyvinyl pyrrolidone (2.5%)
D ₂	-	Polyvinyl pyrrolidone (5%)
D ₃	-	Polyvinyl pyrrolidone (7.5%)
D ₄	-	Polyvinyl pyrrolidone (10%)

CHAPTER ONE

INTRODUCTION

1.1 Pharmaceutical Tablets

Solid formulations are the preparations of pharmaceutical products in their dried, powdered or solid state and these include powders, capsules, granules and tablets. Dosage forms are designed to provide the drug in a suitable form for absorption from each selected route of administration.

Oral administration of drugs is the most frequently used route, simple, convenient and safe. Over 80 % of the drugs formulated to produce systemic effects in the world are produced as oral dosage forms (Rudnic and Kottke, 1999). Oral tablet was introduced as early as 1843 by an Englishman Brockedon, who invented the first hand-operated device for compressed pills. These pills, powders, capsules which were made by hand continued to be in vogue for a long time before the development of the modern pharmaceutical industry and effective production methods.

Tablets are solid pharmaceutical dosage forms containing medicinal drug substances with or without suitable diluents and compressed by means of a tableting machine or by moulding methods (Remington. 2005).

Tablets can also be defined as solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles (European Pharmacopoeia, 2002). The most popular oral dosage forms are tablets, capsules, suspensions, solutions and emulsions, tablets are prepared by compaction and they contain drugs and formulation additives which are included for specific functions (Aulton, 2007).

Capsules are solid dosage forms containing at least a drug substances and usually, appropriate filler(s). The medicament is enclosed in a hard or soft shell composed of gelatin. As with tablets, uniformity of dose can be readily achieved and various sizes, shapes and colours of shell are commercially available.

Suspensions, which contain finely divided drugs suspended in a suitable vehicle, are a useful means of administering large amounts of drugs that would be inconvenient if taken in tablet or capsule form. They are useful for patients who experience difficulty in swallowing tablets and capsules, and are also helpful for pediatric use (Aulton., 2007).

1.2 Stability of Solid Dosage Form

The chemical aspect of formulation generally centres on the chemical stability of the drug and its compatibility with the other formulation ingredients (Pharmpedia, 2010). Drug substances decompose as a result of the effects of heat, oxygen, light and moisture, the presence of moisture is one of the main contributors to degradation of an active drug substance in a pharmaceutical formulation.

Tablets which are usually dry dosage forms contain only minute amounts of water and are chemically more stable than other dosage forms but it cannot be taken for granted in all cases because some additives used in the formulation of tablets are hygroscopic in nature and a little content of moisture can lead to stability problem of the drug, but there are ways to minimize these stability problems. For example, drug substances that are sensitive to hydrolysis can be managed by minimal exposure to moisture during preparation, low moisture content specification in the final product and moisture-resistant packaging can be used.

For oxygen sensitive drugs, an anti-oxidant, can be included in the formulation and as with light-sensitive materials, suitable packaging can reduce or eliminate the problem. Where liquid dosage forms are sensitive to microbial attack, preservatives are required (Aulton, 2007).

1.3 Drug Release from Solid Dosage Forms

A dosage form is usually formulated to aid and/or control the release of drug from it. For example, for an immediate release tablet, the tablet needs to disintegrate to give the primary drug particles immediately after ingestion (Aulton, 2007).

Before a drug can have therapeutic effect, it has to be released from its dosage form into solution and then be absorbed into the systemic blood circulation. However, it is now possible to design a range of different release patterns by changing tablet excipients and/or the manufacturing processes. The site of absorption is also a factor in this aspect, using the oral mucosa as the administration site can improve the speed of both tablet disintegration and drug release and subsequently increase the absorption rate compared with conventional tablets (Odeku, 2005).

1.4 Tablet Manufacturing

Tablets are prepared by forcing particles into close proximity to each other by powder compression, which enables the particles to cohere into a porous, solid specimen of defined geometry. The compression takes place in a die by the action of two punches, the lower and upper, by which the compression force is applied (Alderborn. 2003).

The manufacture of conventional tablets is a cost effective process. Modern tableting machines are able to cater for large scale production. A rotary press can output over 10,000 tablets per minute (Alderborn, 2002).

1.5 Dosage Compliance

The tablet dosage form is convenient to handle, easy and safe for patient administration. It is a well-known and acceptable dosage form. It requires fewer explanatory information and compliance is assumed to be better (Rudnic and Schwartz, 1990).

1.6 Mechanical Strength of Tablets

The mechanical strength of tablet provides a measure of the bonding potential of the material concerned and this information is useful in the selection of excipients. Mechanical properties of pharmaceutical tablets are quantified by the friability, hardness or crushing strength, tensile strength and brittle fracture index (Odeku, 2003). Tablet strength is essential to withstand coating processes, transportation and normal handling by patients. However, the strength of tablets should not be increased at the expense of rapid disintegration and drug release.

Starch is a traditional disintegrant, which is normally used within the range of 2-10 %w/w in a conventional tablet formulation. The starch particles swell moderately in contact with water and the tablet disrupts. Super disintegrants are now commonly used, since these act primarily by extensive swelling, they are effective even in small quantities (Shangraw *et al*, 1989); (Bolhuis *et al*, 1982; Personen *et al*, 1989).

Large particles of disintegrants have been found to swell to a greater extent and with a faster rate than finer particles, resulting in more effective disintegration (Rudnic *et al*, 1982).

1.6.1 Attributes of an Ideal Tablet

The objective of formulation and fabrication of tablet is to deliver the correct amount of drug in the proper form at or over a period of time. Ideal tablet should be free from any visual or functional defects. The general appearance of the tablet, its visual identity and overall “elegance” is essential for consumer acceptance and the control of these general appearances involve measurement of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture, physical flaws and consistency.

- i. Tablet should be elegant having its own identity and free from defects such as
cracks, chips, contaminations, discolorations and so forth
- ii. It should have chemical and physical stability to maintain its physical integrity
over time
- iii. It should be capable of preventing any alteration in the chemical and physical
properties of medicinal agent(s)
- iv. It should be capable of withstanding the rigors of mechanical shocks
encountered in its production, packaging, shipping and dispensing
- v. An ideal tablet should be able to release the medicament(s) in the body in
predictable and reproducible manner.

1.6.2 Types of Tablets

With advancement in technology and increase in awareness towards modifications of standard tablet to achieve better acceptability as well as

bioavailability, newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To understand each dosage form, tablets are classified by their route of administration and type of drugs it contained.

1.6.2.1. Oral Tablets for Ingestion

These tablets are meant to be swallowed intact along with a sufficient quantity of portable water except the tablet is chewable, sublingual tablets etc. Over 90 % of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. Examples are:

- a. Standard compressed tablets
- b. Multiple compressed tablets
 - i. Compression coated tablet
 - ii. Layered tablet
 - iii. Inlay tablet
- c. Modified release tablet
- d. Delayed action tablet
- e. Targeted tablet
 - i. Floating tablet
 - ii. Colon targeting tablet
- F. Chewable tablet

- g. Dispersible tablet

1.6.2.2 Tablets used in the Oral Cavity

The tablets under this group are aimed to release at the oral cavity or to provide local action in this region. The tablets under this category avoid first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in the proper region of oral cavity. Examples are:

- i. Lozenges and troches
- ii. Sublingual tablets
- iii. Buccal tablets
- iv. Dental cones
- v. Mouth dissolved tablets. (Pharmpedia, 2010)

1.6.2.3 Tablets Administered by other Routes

These tablets are administered by route other than the oral cavity and the drugs are designed in a way that they do not pass through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application. Examples are:

- i. Vaginal tablet
- ii. Implant

1.6.3 Advantages of Tablets

- i. Large scale manufacturing is possible.
- ii. Accuracy of dose is maintained.
- iii. Ease of packaging and handling.

- iv. Easy to transport in bulk.
- v. Organoleptic properties are best improved by coating.
- vi. Product identification is easy.

1.6.4 Disadvantages of Tablets

- i. It is difficult to convert high dose poorly compressible active pharmaceutical ingredients into a tablet of suitable size for human use.
- ii. It has slow onset of action as compared to parenteral dosage form.
- iii. Difficult to swallow for kids, terminally ill and geriatric patients.
- iv. Difficult to formulate a drug with poor wettability and slow dissolution into a tablet.
- v. Patients undergoing radiotherapy cannot swallow tablets (Odeku, 2005).

1.7 Pharmaceutical Excipients

The International Pharmaceutical Excipients Council (IPEC) has defined pharmaceutical excipients as substances other than the active drug or pro drug which have been appropriately evaluated for safety and are included in a drug delivery system to either aid in the processing of system during its manufacture; protect, support or enhance stability, bioavailability, or patient acceptability; assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

The role of excipients in determining the quality of a formulation and in many cases the bioavailability of a drug from tablets has received considerable attention in recent years and disintegrants play a significant role in this regard.

Disintegrants expose a greater surface area of tablets to the dissolution medium; hence the disintegrant plays an important role in tablet dissolution before the active drug substance is finally released from the tablet structure into the body. Since a tablet is not useful until its active component is made available for absorption, the disintegrant is arguably the most important excipient in a tablet (Ashford, 2007).

Excipients include disintegrants, diluents, lubricants, suspending agents, emulsifying agents, flavouring agents, colouring agents, emulsifying agents, chemical stabilizers, etc. Excipients are considered to be inert in that they themselves do not exert therapeutic or biological action or modify the biological action of the drug present in the dosage form (Ashford, 2007).

Tablet excipients must meet certain criteria in the formulation such as;

- i. They must be nontoxic and acceptable to the regulatory agencies in all countries where the product is to be marketed
- ii. They must be commercially available in an acceptable grade in all countries where the product is to be manufactured
- iii. Their cost must be acceptably low
- iv. They must be physiologically inert
- v. They must be physically and chemically stable by themselves and in combination with the drug (s) and other tablet components
- vi. They must be free of any unacceptable microbiologic load
- vii. They must be color compatible (not producing any off-color appearance)

- viii. If the drug product is also classified as a food (for example, certain vitamins products), the diluents and other excipients must be approved direct to food additives
- ix. They must have no deleterious effect on the bioavailability of the drug(s) in the product

1.7.1 **Disintegrating Agents**

A tablet disintegrant is that excipient which facilitates the breakup of the tablet in a liquid environment into fine particles prior to dissolution of the active drug and its absorption from the gastro-intestinal tract. Several mechanisms have been proposed to rationalize the action of disintegrants and these include porosity and capillary action, rate of water uptake into the tablet, swelling of disintegrants particles, gas release, melting and enzymatic action, heat of wetting and lysis of physico-chemical bonds (Kanig and Rudnic. 1984). There is constant pressure to search for new excipients to attain the desired set of functionalities. Improved functionality of excipients can be obtained by developing new excipients, new grades fillers, binders and so forth.

1.7.2 **Glidant, Antiadherent and lubricant**

Glidant are added to increase the flowability of the powder mass, reduce interparticulate friction and improve powder flow in the hopper shoe and die of the tableting machine. An antiadherent can be added to decrease sticking of the powder to the faces of the punches and die walls during compaction. Examples are talc, magnesium stearate and so forth.

Disintegrants, wetting agents, anti-oxidants, preservatives, colouring and flavouring agents help to give desirable physical characteristics to the finished tablets.

1.7.3 Colouring and Flavouring Agents

Colouring and flavouring agents are used in disguising of off colour drugs, product identification and production of a more elegant product. Colouring tablets also have aesthetic value and can improve tablet identification especially when patients are taking a number of different tablets.

1.7.4 Fillers/Diluents

Fillers are materials which are used to make tablets of sufficient size for easy handling by the patient and to facilitate production. For example, a tablet containing very potent active substances for example, Digoxin, would be too small to be handling without additional excipients. Good filler should possess good compatibility, good flow properties, acceptable taste, be non-hygroscopic and preferably chemically inert (Gideon *et al*, 2011).

1.7.5 Pharmaceutical Binders

These are materials added either in dry or in liquid form to form granules or to promote cohesive compacts for directly compressed tablets. These include natural gums, alginic and alginate, starches, liquid glucose, cellulose derivatives and polyvinylpyrrolidone (PVP) (Odeku. 2005).

Binders can be defined as agents used to impart cohesive qualities to the powdered material during the production of tablets. They impart cohesiveness to the tablet formulation, which ensures that the tablet remains intact after compression as well as improving the free flowing quality (Gideon *et al*, 2011).

Binders have been used as solutions and in dry form depending on the other ingredients in the formulations and the method of preparation. The choice of a particular binding agent depends on the binding force required to form granules and its compatibility with the other ingredients particularly the active drug (Olorunsola *et al* 2013). Starches from different sources have been evaluated and used as excellent binders in either mucilage or the dry powdered. Maize and potato starches have been in common use and recently cassava starch too, has appeared in the British Pharmacopoeia as an official starch for use as a binder (British Pharmacopoeia, 2001). Their use has increased in the tropics where previously recognized starches are unavailable. Most binding agents are hydrophilic in nature; they increase the bulk density and reduce the porosity of the powder, thereby diminishing the effective surface area of evaporation. Increase in binder concentration leads to increase in mean particle size, harder granules, decreased granule flowability and decrease in tapped density and hence reduction in granule porosity.

PVP is a synthetic polymer that is used as an adhesive in either an aqueous solution or alcohol. Its versatility has increased its popularity. Its useful concentration ranges from 0.5 to 5 % solution.

Binders are added to materials to increase bonding. Granulation with a more homogenous distribution of binder in the granules generally produces tablets of a higher mechanical strength than granulation with peripheral localization of binder. Adequate mixing is needed for homogenous distribution of the excipients and satisfactory result.

Granules with higher amount of fine and larger particles size distribution generally have poor flow from hopper and are likely to cause weight variation of dosage form. Preformulation studies demonstrate their influence on stability, bioavailability and the process by which the dosage form ought to be prepared. Modifications using physical, chemical or bio-chemical method have led to numerous highly functional derivatives which have enabled the evolution of new processing technologies and market trends. To this end, speciality starches have been tailored to create a competitive advantage in a new product, enhance product aesthetics, simplify label declaration, reduce recipe/production costs, increase product throughput, eradicate batch rejects, ensure product consistency, and extend shelf life. Clearly, understanding the capabilities of starch and how to exploit its potential is of relevance to all stages of food / pharmaceutical product's life cycle from development, through production and marketing, to retail.

Native starches have been used for a long time in food and find vast industrial application (Apeji. 2010). Starch continues to be attractive as a binding material because of its abundant supply, low cost, biodegradability and ease of chemical modification. Starches are used extensively in pharmaceutical industries as disintegrants, binders and lubricants in tablet formulation. Some authors have studied the use of starch obtained from different novel sources like, Godare, ginger and yam as binders and disintegrants in solid dosage formulation (Adane. 2006, Ibezim. 2008).

It is quite apparent that there is a relationship between properties of excipients and the dosage form containing them.

The characterization of pharmaceutical excipients using a material science approach has helped to design drug formulations to obtain a desired set of performance and properties. For tablets, a better understanding of the compression properties of the material alone and in combination with other potential components helps in developing desirable formulation as well as acceptable products.

When formulating tablets, the choice of excipients is extremely critical, It must fulfill certain requirements such as good binding functionality, powder crystallinity, flowability and acceptable moisture content. Also it is essential to have a well-designed particle size distribution for favourable mixing of excipients with drugs.

1.8 Volume Reduction of Pharmaceutical Powders

In pharmaceutical sciences, the relationship between volume and applied pressure during compression is the main approach to deriving a mathematical representation of the compression process (Alderborn, 2002). During compression of powders, the force applied results in reducing the distance between the punches, while the powder bed decreases in volume. The volume reduction mechanism that dominates during compression is dependent on the properties of the component materials. In fact, there is usually more than one mechanism involved.

Under initial low pressures in the die, the powder particles rearrange to form a more closely packed structure; the voids between the particles are reduced in size and the porosity of the tablet unit decreases. At a certain load, the reduced space and the increased interparticulate friction will prevent any further interparticulate movement; the subsequent reduction of the tablet volume is therefore associated with changes in the dimensions of the particle (Alderborn, 2003).

Pharmaceutical materials which mainly consist of organic compounds with complex particles structures sometimes undergo limited initial elastic/plastic deformation and then extensive particle fragmentation at low pressures, followed by a second deformation and then extensive particles fragmentation at low pressures involving the newly formed smaller particles at higher load.

This effect is especially pronounced for pharmaceutical materials composed of aggregate of primary particles or highly porous particles, which after the initial fragmentation undergo plastic or elastic deformation at higher compaction loads (Duberg and Nystrom, 1985). After the maximum load has been reached, the compaction pressure is gradually released. If the material has undergone extensive elastic deformation, the tablet will expand, which can cause breakage of interparticulate bonds and possibly capping of the tablet. Heckel and Kawakita equations are some of the models which are used to describe the compression of powders.

1.9 Bonding in tablet

The transformation of a powder into a tablet is fundamentally an interparticulate bonding process. The nature of these bonds is traditionally subdivided into five types, known as the Rumpf classification and they are as follows;

- i. Solid bridges
- ii. Bonding by liquids (capillary and surface tension forces)
- iii. Binder bridges (viscous binders and adsorption layers)
- iv. Intermolecular and electrostatic forces
- v. Mechanical interlocking

The formation of solid bridges, also referred to as the diffusion theory of bonding occurs when two solids are mixed at their interface and accordingly form a continuous solid phase (Alderborn, 2003).

Granules are secondary particles formed by the agglomeration of primary particles and they are handled in a tableting operation. When granules are compacted, bonds will be formed between adjacent granule surfaces. Granules often include a binder. When such binder – substrate granules are compacted, it is reasonable to assume that the binder also plays an important role in the formation of intergranular bonds. The binder may fuse together locally and form binder bridges between granule surfaces which coheres the granules to each other. Such bridges may be the result of a softening or melting of binder layers during the compression phase.

1.10 The process of compaction

Compaction is fundamentally a bonding process, that is, it is the strength provided by bonds formed at the interparticulate junctions or contact sites during the compression process. Studies on the structure of fractured tablets indicate that a tablet generally fails by the breakage of interparticulate bonds, that is, an interparticulate fracture process (Alderborn, 2003). However, especially for tablets of low porosity, the tablet can also fracture by breakage of the particles that form the tablet (Alderborn, and Nystrom, 1996).

Direct compaction of tablet production reduces production time and cost as it minimize the number of operations involved in the pretreatment of the powder mixture before tableting. There are two operations involved in tableting and they include powder mixing and tableting. They require a larger number of quality tests

before processing. Heat and water are not involved hence product stability can be improved. Drug dissolution might be faster from a tablet prepared by direct compaction owing to fast tablet disintegration into primary drug particle (Alderborn, 2003).

1.11 Factors that affect Drug Release from Tablets

The two basic mechanisms controlling drug release are dissolution of the active drug component and the diffusion of dissolved or solubilized species.

Drug release system can be designed to have either continuous release or delayed release and it may be constant, declining or bimodal.

- i. **Constant Release:** This is the general belief that the ideal drug release should provide and maintain constant drug plasma concentrations.
- ii. **Declining Release:** Drug release is a function of the square root of time, it can be said that it follows first-order kinetics. The system cannot maintain a constant plasma drug concentration but can provide sustained release (Collett and Moreton, 2002).

Other potential rate limiting steps are wetting of the tablet, penetration of liquid into the tablet structure, disintegration of the tablet. It is therefore very important to identify and learn how to modify the factors affecting the processes of drug release, so that improved tablet designs for fast release and absorption of drug can be developed.

1.11.1 Wetting

The generally acceptable wetting is normally obtained by the use of fillers, binders or disintegrating excipients which also possess hydrophilic properties. Examples of hydrophobic excipients are stearates (Lerk *et al*, 1986) while that of

brittle excipients are crystalline lactose, sugar alcohols and inorganic salts (Alderborn *et al.* 1985; Duberg and Nyström, 1986).

1.11.2 **Water Penetration**

Liquid penetration is enhanced by improving wetting, or decreasing the surface tension, keeping the viscosity of the penetrating liquid low and increasing the average pore diameter. After applying these factors in relation to wetting, any unnecessary surfactants should be removed from the formulation (Nogami *et al.*, 1963).

The pore structure is affected by the choice of excipients. Liquid penetration is thought to be influenced by the porosity of the tablets, which is determined by such factors as compaction load and the properties of the constituent materials (Shangraw *et al.*, 1980).

1.11.3 **Disintegration**

The main mechanism involve swelling of the disintegrant particles which rupture the tablet and disintegrants which facilitates water uptake through capillary action or wicking, that is, the disintegrants draw water up into the porous network of the tablet which reduces the physical bonding forces between particles with the consequence that the tablet may break into fragments (Alderborn, 2003).

Other mechanisms include deformation of disintegrant particles and tablet rupture (Alderborn, 2003). Wetting and rate of liquid penetration into the pores within the tablets will influence the disintegration time. A disintegrant is included in the formulation to ensure that the tablet, when in contact with a liquid, breaks up into small fragments, which promotes rapid drug dissolution. Ideally, the tablet

should break up into individual drug particles in order to obtain the largest possible effective surface area during dissolution (Alderborn, 2003).

1.12 Dissolution

This is the transfer of molecules or ions from a solid state into solution. This process is controlled by the relative affinity between the molecules of the solid substance and those of the solvent (Aulton, 2007). Majority of drugs and excipients are crystalline solids. Dissolution can be said to have two consecutive stages.

1.12.1. Interfacial Reaction

This results in the liberation of solute molecules from the solid phase to the liquid phase, this involves a phase change so that molecules of solid become molecules of solute in the solvent in which the crystal is dissolving, that is, replacement of crystal molecules by solvent molecules.

1.12.2. Diffusion through the boundary layer

The solute molecules must migrate through the boundary layers surrounding the crystal to the bulk of solution (Aulton, 2007). It does not necessarily follow that whenever a tablet disintegrates quickly into smaller particles, there will be dissolution.

The main method of increasing the exposure of drug particle surface area is to use very finely divided grades of drug while making sure that the added excipients do not separate the dissolving liquid from the drug particles. To achieve this, freeze-drying, which is a known principle is used to obtain highly porous tablets. It promotes rapid exposure of drug phase and thus drug dissolution can be achieved. Water-soluble excipients can also be used (Corveley and Renon, 1998).

1.13. Enzyme Hydrolysis

Starch and modified starches have been widely and safely used with approval from the National agency for Food and Drug administration and control (NAFDAC) in food and pharmaceutical industries. It is used in food industries as thickeners, enhancer of organoleptic properties and texture modifiers while in pharmaceuticals it is used as filler, binder and disintegrant.

Starch is the most common carbohydrate found in plants. It is used by the plants themselves, microbes and by other higher organisms too. There is a great diversity of enzymes that are able to catalyze its hydrolysis for example α -amylase, β -amylase, glucoamylase, pullulanase, etc.

Amylolysis is the breakdown of the starch granules by the action of the enzyme α -amylase. This enzyme is a bacterium, an endoenzyme. It catalyses the hydrolysis of α (1, 4) glucosidic linkages located in the inner region of the starch molecules, amylose, amylopectin and related oligosaccharides. This causes their fission into glucose, maltose or smaller dextrin molecules by the multiple attack mechanism. Dissolved or gelatinized forms of natural starches react rapidly towards α -amylase and the reaction rate of raw or granular forms are much slower and varying according to sources of the starch.

In order to improve native starch, enzymatic methods have been employed. Enzymatic modification improves the flowability and compressibility profile of starch. The use of enzymes to improve the quality of starch is much safer and cheaper unlike acid hydrolysis of starch which though gained ground in the past is now being replaced by enzymatic processes. Enzymatic hydrolysis does not require

the use of corrosive materials which gave rise to high colour and salt/ash content (after neutralization). Acid hydrolysis needs more energy exposure for heating and is relatively difficult to control (Olorunsola, 2011).

Enzymes are capable of speeding up the rate of biological reactions up to 10 folds and they are specific in hydrolysis. Enzymatic hydrolysis has gradually gained popularity over acid hydrolysis (a form of chemical modification where the glycosidic bonds of the starch are broken in the presence of acid leading to the formation of mixtures of anomeric sugars. Acid hydrolysis is a non-specific process in that any form of the glycosidic bond can be broken unlike enzyme hydrolysis which are specific, for example α -amylase from *Bacillus amyloliquefaciens* is specific for α -1, 4-glycosidic bond, glucoamylase from *Aspergillus niger* act on α - 1,4 and α 1,6 linkages, pullulanase from *Bacillus acidopullulyticus* is specific for α 1,6 – glycosidic linkage. Modifications have been shown to improve the compressibility, compactibility and flow of native starch (Apeji, 2010).

The action of α -amylase with starch granules occur via the following steps;

- a. Diffusion to the solid surface
- b. Adsorption (prerequisite step for subsequent catalytic activity)
- c. Catalysis

In general, enzymes either erode the entire granule surface or sections of it (exocorrosion) or digest channels from selected points on the surface towards the centre of the granule (endocorrosion) (Gallant *et al.* 1992).

1.14. **Enzyme hydrolyzed starch**

The use of enzyme improves the Physico chemical properties of starch. The enzyme preferentially attacks the amorphous growth ring and this is because the amorphous region will be attacked more readily than the semi crystalline rings (Apeji, 2010). Gallant *et al*,(1994) reported the difference in the mode of action of enzyme on small and large commercial corn and cassava starch granules. Enzymatic attacks on the larger granules occurs at a slower rate and proceeds by pin holes on the surface and surface corrosion, mainly at the radial axis and then the enzyme apparently hydrolyses the granules from inside. For small size granules, the enzymatic action is restricted to the surface and was characterized by erosion accompanied by solubilisation of the granules.

These results suggest that the components of small and large granules differ structurally from one another. The uses of enzymes in processing starch, typical conditions are given in literature. There are three stages in the modification of starch;

- a. Gelatinization, involving the dissolution of the nanogram sized starch granules to form a viscous suspension
- b. Liquefaction, involving the partial hydrolysis of the starch, with concomitant loss in viscosity and
- c. Saccharification, involving the production of glucose and maltose by further hydrolysis.

TABLE 1.1: TYPE OF ENZYMES USED IN STARCH HYDROLYSIS (Adapted from file,\\G:\Starch.html 2004)

Enzyme	EC Number	Source	Action
α -Amylase	3.2.1.1	<i>Bacillus amyloliquefeciens</i>	Only α -1,4 oligosaccharide links are cleaved to give α -dextrins and predominantly maltose (G2), G3, G6 and G7 oligosaccharides
		<i>B. licheniformis</i>	Only α -1,4 oligosaccharide links are cleaved to give α -dextrins and predominantly maltose, G3, G4 and G5 oligosaccharides
		<i>Aspergillus oryzeae</i> , <i>A. niger</i>	Only α -1,4 oligosaccharide links are cleaved to give α -dextrins and predominantly maltose and G3, oligosaccharides
Saccharifying α -amylase	3.2.1.1	<i>B. subtilis</i> (<i>amylosacchariticus</i>)	Only α 1,4 – oligosaccharide links are cleaved to give α -dextrins with maltose, G3, G4 and up to 50% (w/w) glucose
β -Amylase	3.2.1.2	Malted barley	Only α 1,4 links are cleaved from non-reducing ends, to give limit dextrins and β maltose
Glucoamylase	3.2.1.3	<i>A. niger</i>	α - 1,4 and 1,6 links are cleaved from the non-reducing ends, to give glucose β
Pullulanase	3.2.1.4.1	<i>B. acidopullulyticus</i>	Only α - 1,6 links are cleaved to give straight-chain maltodextrins.

1.15 Statement of Research Problem

In Nigeria, production of drugs depends on the importation of raw materials and sometimes even finished products; this has therefore led to the depletion of foreign exchange and subsequently unavailability of jobs, precipitating poverty and poor social development.

Recently, the African union (AU) commission at the Abuja summit in January, 2005 gave its members a mandate to explore local production of generic medicines in Africa, promote local production of finished goods and raw materials, so that there will be improved foreign exchange reserve, availability of jobs, facilitation of technology transfer and increase in products exports, since raw materials sourced locally will be in abundance and hence cheap.

Starch is locally available in Nigeria and its use should be explored as raw materials in food and pharmaceutical industries. Native starch despite its usefulness has poor physico-chemical properties like poor compressibility, poor flowability, ability to generate dust, etc. Hence it cannot be adopted as such for use as excipients for direct compression, it has become very important therefore to modify starch to improve its properties.

1.16 Justification of the Study

The Federal Government has laid emphasis on the use of local raw materials in manufacturing as this will lead to conservation of foreign exchange, availability of jobs, and self-reliance from importation.

Although cassava is cultivated in most parts of Nigeria, and it is widely available in large quantity, it is mainly used for human consumption. With the

increase in demand for starch as a pharmaceutical excipient, it can be processed to make ethanol and starch.

1.17 **Research Hypothesis**

Null: There is no difference in the binding properties of NCS and EHS in Chloroquine Phosphate tablet formulations.

Alternate: The binding property of EHS is better than that of NCS in Chloroquine Phosphate tablet formulations.

1.18 **Aim**

The aim of this study is to evaluate the suitability of Enzyme – hydrolyzed cassava starch as binder in chloroquine phosphate tablet formulations.

1.19 **OBJECTIVES**

- i. To extract starch from cassava tubers
- ii. To produce enzyme- hydrolyzed starch through the action of α -amylase on the extracted starch
- iii. To determine the physico-chemical properties and characterize the modified starch
- iv. To formulate chloroquine tablets using enzyme- hydrolyzed starch at varying binder concentrations by wet granulation and direct compression methods
- v. To evaluate the tablet properties of tablets produced using the starch
- vi. To study the compaction behaviour of the modified starch and the chloroquine tablet formulations.

1.20. **Scope of Work**

- i. Collection and identification of cassava tubers
- ii. Extraction of starch from cassava tuber
- iii. Production of Enzyme -hydrolyzed cassava starch
- iv. Evaluation of the Physico-chemical properties of the enzyme - hydrolyzed starch
- v. Formulation of tablets by wet granulation and direct compression methods using the enzyme hydrolyzed starch.

CHAPTER TWO

LITERATURE REVIEW

2.1 Starch

Starch is one of the most widely used excipients in the manufacture of solid dosage forms. It can be used as filler, binder, disintegrant and glidant. It is of great commercial importance because of its inertness, abundance and cheapness (Alebiowu and Itiola. 2003). It is next to cellulose in natural abundance. It may be digested by human and most animals but cellulose is not digestible because of its structural complexity.

Starch is the main carbohydrate in plants and acts as a reserve food supply for the plants over periods of growth, dormancy and germination. Whenever starch is digested, the trapped energy is released. It is broken down by hydrolysis to glucose molecules and further to carbon dioxide and water (Gideon. 2011).

The extraction of starch from its parent body occurs in different ways for example the extraction of maize starch from maize kernel is called wet milling and the objective of extraction is to obtain insoluble starch with undamaged and or intact granules which can be washed, dried and stored for further modifications.

Starch obtained from different botanical sources may not have identical properties with respect to their uses for specific pharmaceutical purposes for example, maize, rice, wheat. Starches are principal food reserve polysaccharides in the plant kingdom. They form the major source of carbohydrate in human diet and are therefore of great economic importance. Starches obtained from grains and roots have been consumed as food for many centuries. It is a very versatile raw material and finds applications. It exists in granular form and the shapes of the granules are

characteristics of the source of the starch. Starch is made up of two components amylose and amylopectin (Olorunsola, 2011).

The granule size is known to influence the disintegration of tablets containing starch. The smaller the granule size, the faster is the disintegration process because more pores are made available for the penetration of water into the tablet. Amylose is a linear polymer containing up to 6000 glucose units connected by α -1, 4 linkages (Apeji, 2010). It is insoluble in cold water but absorbs a large quantity of water and swells. There are greater tendencies in the starch industries towards the utilization of raw material other than maize and potatoes, their starches have been in common use and recently cassava starch appeared in the B.P as an official starch for use as binder (B.P 2002). Nigeria has many native species, which can be used as sources of starch for pharmaceutical purposes. it is one of the most actively marketed food product and is the most promising in term of growth and new market opportunity.

Several Governments in Nigeria have taken positive steps to promote cassava production for industrial processing since it has large capacity for the cultivation and processing of cassava (Mohammed *et al.* 2009).

Starch is a polysaccharide with a large number of glucose molecules. It is widely distributed in different parts of plants. The United States pharmacopoeia (USP) grade starch may be obtained from either the grains of rice, corn, wheat, tubers of cassava and potato. Other sources include sorghum, millet, sago and yam. Starch finds a wide application in the production of pharmaceuticals. Its use is

based on its adhesive, thickening, gelling, swelling and film-forming properties as well as its ready availability, low cost and controlled quality.

The whiteness and relative free flowability of starch in its native form makes it attractive excipients for pharmaceutical formulation. However, due to certain limitations of native form such as poor compressibility and flow properties, several physical, chemical and enzymatic modifications have improved the functional properties of starches allowing a wide range of its application (Tharanathan, 2005).

In recent years, pharmaceutical scientist have been paying increasing attention to the extraction, development and use of starches in the formulation of dosage forms (Singh and Nath, 2012; Ogaji, 2011)

2.2 Morphology of cassava starch

Cassava starch granules are mostly round with a flat surface on one side containing a conical pit which extends to well-defined eccentric helium; it has a granule size of diameter which ranges 5 – 25 μm . The native surface of most granules appears smooth without observation pores (Apeji, 2010).

Starch can undergo modification by cross linking, application of heat leading to breaking up of long glucose chains into simpler molecules like dextrin, polydextrin and maltodextrin. Starches can also have their hydrogen atom replaced by a carboxymethyl group to form a carboxymethyl starch which is less prone to damage by heat and bacteria. It is also more hydrophilic and aids in cross-linking.

Starch consists of two types of molecule, amylose (20–30 %) and amylopectin (70–80 %), both having polymers of D – glucose units. It is versatile,

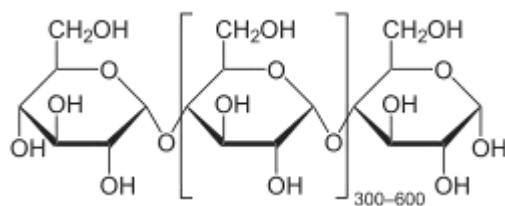
inexpensive, stable, safe, non-toxic and it has good film forming properties and is biodegradable (Apeji, 2010).



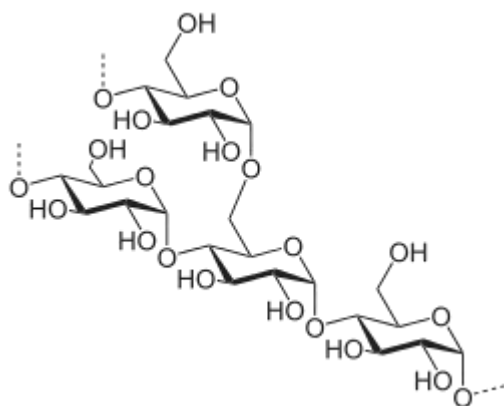
Plate 1.0: Cassava roots



Plate 1.1: Cassava leaf



STRUCTURE OF THE AMYLOSE MOLECULE



STRUCTURE OF THE AMYLOPECTIN MOLECULE (Adapted from <http://en.wikipedia.org/wiki/file>, 2008).

2.3 Gelatinization

This is the term used to describe the molecular events associated with the heating of starch in water. Starch is converted from a semi crystalline, relatively indigestible form to an amorphous (readily digestible) form. The gelatinization process is believed to involve primary hydration of amorphous region around and above glass temperature with an associated glassy – rubbery transition; this in turn facilitates molecules mobility in the amorphous regions which then provokes an irreversible molecular transition (Apeji, 2010).

Cassava with the botanical names *Manihot esculenta* (bitter cassava) and *Manihot utilissima* or *Manihot aipi*. It is also called manioc, tapioca or yuch (Family Euphorbiaceae), it is an economic crop. Cassava is a plant that has been

processed into many products and they are still emerging new products from cassava. These products have fed millions of people and others have economic value, this has elicited in cassava based product research (Ukwuru *et al.*, 2013). Cassava roots comprise of the peel and bulky storage with a heavy concentration of carbohydrate of about 80 % and 2-4 % crude proteins on dry weight basis (Falade and Akingbala, 2011)

Cassava starch is a staple food consumed in both rural and urban areas of Nigeria, a country with a population of about 170 million people. In recent years, it has also been transformed from being a subsistent crop to industrial cash crop (Mohammed *et al.*, 2009).

Most cassava starch is sourced from Brazil, Thailand, Indonesia, and now Nigeria. It is a leading food and feed plant. Brazil is the first largest producer and the first consumer all over the World (Nassar *et al.*, 2002; FAO 2005).

It is called Akpu by the Igbos, Ege by the Yoruba and Rogo by the Hausas and Gwaris. It is one of the most staple food crops in the humid tropics. It is widely cultivated in all parts of Nigeria, has the ability to survive drought and it can thrive well in most types of soil.

Cassava tubers are a potential starch source that can be used in food, paper, adhesive, alcohols, animal feeds, textiles and pharmaceutical industries. Cassava roots contain high starch content and low quantity of impurities like protein and lipids. The cassava tubers contain carbohydrate 40 times than rice and 25 times than maize and are far cheaper than rice and maize.

Cassava starch has characteristics of odourless, paste, clarity and stickiness. These remarkable characteristics of cassava starch are enabling factors which allow

it to be conveniently and readily blended with other flavouring and colouring agents. It is fine in texture and creaks when pressed between the fingers (Upendra, 2010).

2.4 Varieties and Properties of Starch Granules

Native starches differ in the amylose/amylopectin ratio depending on their botanical source. For example, native starches are composed of 20–30 % amylose and about 70–80 % of amylopectin. Amylose – enriched starch may contain up to 84 % amylose while waxy starches consist of nearly pure amylopectin. Native starches obtained from renewable sources are natural polymers with anhydroglucose units (Joshi and Neves, 2005).

2.5 Starch Modifications

Starch modifications are means of altering the structures and affecting the hydrogen bonding in a controllable manner to enhance and extend their applications. These modifications can be through chemical, physical and or biochemical modification. It has been shown to improve the compressibility, compactibility and flow rate of native starch (Apeji, 2010).

Modifications only take place at the molecular level with little superficial appearance of the granule. Below are some modifications that take place. Physical and Chemical modification have been used to improve the compaction properties of some Native starches (Odeku *et al.* 2008).

2.5.1 Acid Hydrolysis of starch

This is a form of chemical modification; here the glycosidic bonds of the starch are broken in the presence of acid leading to the formation of mixtures of anomeric sugars. It is nonspecific in that any form of the glycosidic bond can be broken. The acid predominantly attacks and depolymerizes the amorphous regions of the granule such that when the starch is heated beyond its gelatinization temperature, the granules rupture quickly.

Acid modified starches have been used as filler binder in a production of pharmaceutical tablets (Puchongkavarin *et al* 2003)

2.5.2 Cross – Linking

Cross-linking is one of the most important chemical modifications. It involves replacement of the hydrogen bonding between starch chains by stronger, more permanent, covalent bonds. Here the swelling of the starch granule is inhibited, pre-empting disintegration either by chemical attack, mechanical attrition or cooking. Cross-linking is often performed in combination with esterification and this provides appropriate gelatinization, viscosity and texture properties (Huijbrechts, 2008).

2.5.3 Stabilization

This process is usually carried out in conjunction with cross-linking. The bulky groups are usually substituted onto the starch in order to take up space and hinder (that is, cause steric hindrance) any tendency for dispersed, linear fragments to re-align and retrograde. The primary objective is to prevent retrogradation and enhance shelf life through tolerance to temperature fluctuation such as freeze – thaw cycles.

2.5.4 **Enzyme Hydrolysis**

This is a form of biochemical modification where enzymes are used for breaking up of the straight chains and or the branched chain of the starch, for example, α - amylase selectively and randomly attacks the 1, 4 – linkages of starch to produce maltodextrin. Other enzymes are iso-amylase, pullulanase; they improve the functionality of the native starch.

2.5.5 **Pregelatinization**

This is a physical modification. Some starches require cooking to develop or improve their functionalities but with pregelatinization there will be no need for cooking. It is used to achieve a versatile range of cold thickening starches. The starch is pre-cooked or instantised by simultaneously cooking and drying using one of the following processes;

- i. Drum drying
- ii. Extrusion and
- iii. Spray drying method.

2.5.6 **Annealing**

This is a physical modification whereby the starch is incubated in excess water (≥ 60 % w/w) or intermediate water content (40 to 55 % w/w) at a temperature between the glass temperature and the gelatinization temperature for a certain period of time (Tukomane, 2008). It modifies the physicochemical properties of starch without destroying the granular structure.

2.6 Recent Studies on Modified Starches

Native starch is one of the most widely used excipients in the manufacture of solid dosage forms (Isah *et al*, 2012). It can be used as filler, binder, disintegrant and glidant (Apeji, 2010). In recent years, Pharmaceutical scientists have been paying increasing attention to the extraction, development and use of starch in the formulation of dosage forms (Ogaji, 2011). However, due to its limitations it has to be modified.

Emmanuel *et al* (2013) carried out a study on the influence of compaction pressures on the quality of tablets from formulations containing native and microcrystalline sweet potato starches using acid hydrolysis, it was discovered that both starches are more suitable than Maize starch BP. as binder for use in high speed tableting machine with short dwell time, they both tolerated high compaction pressure and possess good release properties.

In a study carried out by Odeku and Itiola (2007), it was reported that various researchers have noted that maize, potato, rice and cassava are good sources of starch useful as excipients in tableting. A study carried out by Apeji *et al* (2011) on formulation and evaluation of Ascorbic acid tablet by direct compression using microcrystalline starch as a direct compression excipient. The result indicated that modification of native starch by Enzyme hydrolysis imparted some desirable features required for direct compression hence it can be employed as a direct compressible excipient in tablet formulations containing heat or moisture sensitive drug by direct compression.

Shittu *et al.*, (2012) carried out formulation and evaluation of A-2 component composite excipient 'Microcrystarlac' as a filler-binder for direct compression and

it was reported that the starch can be employed preferably to formulate hard tablet especially poorly soluble and compressible API. A study was carried out by Huaxiao *et al* (2012) on comparative characteristics of cross-linked, oxidized and dual-modified rice starches and it was reported that there was no significant effect on the morphological properties of rice starch granules.

Alebiowu *et al* (2003) reported a decrease in disintegration time of tablets when changing from a native to a pregelatinized starch as disintegrant. A study was carried out by Anwar *et al* (2006) on pregelatinized cassava starch phosphate as hydrophilic polymer excipients for controlled release tablets. The result showed that pregelatinised cassava starch phosphate was a suitable material for matrix tablet controlled release.

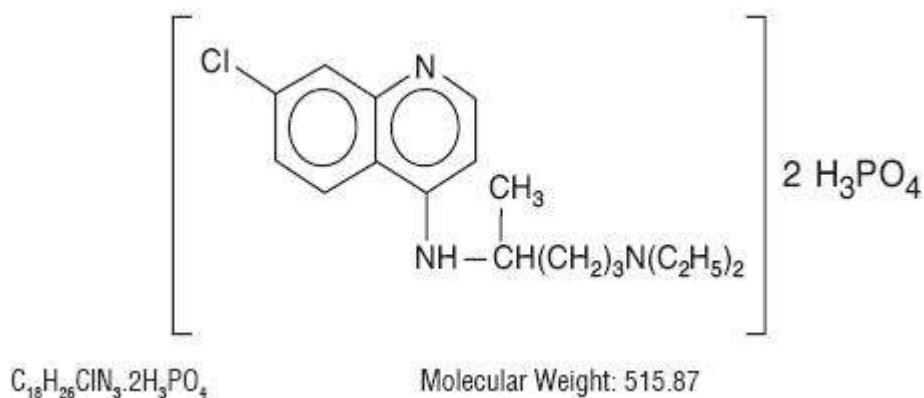
Tukomane *et al* (2007) studied the effect of annealed enzymatic hydrolyzed tapioca starch on tablet production and the result showed improvement in the crushing strength of the tablet produced, and this was associated with a significant decrease in amylose content after prolonged hydrolysis.

Aiyer, (2005) carried out study on modified starches and reported that modified starches with improved functional properties have been derived using conventional physical and chemical methods but the use of Enzymatic hydrolysis is more specific in its action and so fewer byproducts are formed with a greater percentage yield.

2.7 Chloroquine Phosphate

Chloroquine phosphate is an important antimalarial drug. It is used as the model drug, it is a relatively high dose, water soluble and a poorly compressible soluble drug which requires a binding agent among other excipients to form

satisfactorily strong drug. It is generally administered as tablet containing 250 mg of active drug with appropriate quantity of excipients. It is usually formulated by wet granulation technique, but attempt has been made to formulate the drug by direct compression technique using the modified starch as a binder (Okunola and Odeku. 2011).



Structure adapted from <http://www.medicineonline.com/drugs/C/2468> 2003.

2.8 Granulation

This may be defined *as* a size enlargement process which converts small particles into physically stronger and larger agglomerates and for the powder mixture to flow evenly and freely from the hopper into the die. It is necessary to convert the powder mixture to free flowing granules in order to ensure uniformity of dose, prevent segregation of ingredients in the hopper of the tableting machine and improve the compression characteristics of the tablet mixture.

Granulation method can be broadly classified into three types: wet granulation, dry granulation, and dry granulation incorporating bound moisture (Staniforth and Aulton, 2007).

2.9 Wet Granulation

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

2.9.1 Important Steps involved in the wet granulation

- i. Mixing of the drug(s) and excipients
- ii. Preparation of binder solution
- iii. Mixing of binder solution with powder mixture to form wet mass
- iv. Coarse screening of wet mass using a suitable sieve (6-12 # screen)
- v. Drying of moist granules
- vi. Screening of dry granules through a suitable sieve (14-20 # screen)
- vii. Mixing of screened granules with disintegrant, glidant, and lubricant

2.9.2 Limitation of wet granulation

- i. The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labour, time, equipment, energy and space requirements
- ii. Loss of material during various stages of processing
- iii. Stability may be a major concern for moisture sensitive or thermo-labile drugs
- iv. Multiple processing steps add complexity and make validation and control difficult
- vi. An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

2.10 **Special wet granulation techniques**

- i. High shear mixture granulation
- ii. Fluid bed granulation
- ii. Extrusion-spheronization
- iii. Spray drying

2.10.1 **High shear mixture granulation**

High shear mixture has been widely used in pharmaceutical industries for blending and granulation. Blending and wet massing is accompanied by high mechanical agitation by an impeller and a chopper. Mixing, densification and agglomeration are achieved through shear and compaction force exerted by the impeller.

2.10.1.1 **Advantages**

- i. Short processing time
- ii. Less amount of liquid binders required compared with fluid bed
- iv. Highly cohesive material can be granulated.

2.10.2 **Fluid bed granulation**

Fluidization is the operation by which fine solids are transformed into a fluid like state through contact with a gas. At certain gas velocity the fluid will support the particles giving them free mobility without entrapment.

Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed. The materials processed by fluid bed granulation are finer, free flowing and homogenous (Pharmpedia, 2010).

2.10.3 **Extrusion and Spheronization**

It is a multiple step process capable of making uniform sized spherical particles, it is primarily used as a method to produce multi-particulates for controlled release application.

2.10.3.1 **Advantages:**

- i. Ability to incorporate higher levels of active components without producing excessively larger particles
- iii. Application to both immediate and controlled release dosage form.

2.10.4 **Spray drying granulation**

It is a unique granulation technique that directly converts liquids into dry powder in a single step. This method removes moisture instantly and converts pumpable liquids into a dry powder.

2.10.4.1 **Advantages**

- i. Rapid process.
- ii. Ability to be operated continuously.
- iii. Suitable for heat sensitive drugs.

2.11. **Dry Granulation**

In dry granulation process, the powder mixture is compressed without the use of heat and liquid solvent. It is the least desirable of all methods of granulation. The two basic procedures are, to form a compact of material by compression and then to mill the compact to obtain granules.

Two methods are used for dry granulation, the most widely used method is slugging, where the powder is recompressed and the resulting tablet or slug are

milled to yield the granules. The other method is to recompress the powder with pressure rolls using a machine such as Chilsonator.

2.11.1 **Advantages**

The main advantages of dry granulation or slugging are that it uses less equipment and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

- i. For moisture sensitive materials.
- ii. For heat sensitive materials.
- iii. For improved disintegration since powder particles are not bonded together by a binder.

2.11.2 **Disadvantages**

- i. It requires a specialized heavy duty tablets press to form slug.
- ii. It does not permit uniform colour distribution achieved with wet granulation where the dye can be incorporated into binder liquid
- iii. The process tends to create more dust than wet granulation, increasing the potential contamination.

2.12 **Steps in Dry Granulation**

- i. Milling of drugs and excipients.
- ii. Mixing of milled powders.
- iii. Compression into large, hard tablets to make slugs.
- iv. Screening of slugs.
- v. Mixing with lubricant and disintegrating agent.
- vi. Tablet compression.

2.13 Commonly used Dry Granulation Processes

2.13.1 Slugging process

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slugs should be monitored. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

2.13.1.1 Factors which determine how well a material may slug

- i. Compressibility or cohesiveness of the material
- ii. Compression ratio of powder
- iii. Density of the powder
- iv. Machine type
- v. Punch and die size
- vi. Slug thickness
- vii. Speed of compression
- viii. Pressure used to produce slug (www.pharmainfo.net)

2.13.2 Roller Compaction

The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

2.14 **Dry Granulation**

The excipients used for dry granulation are basically same as that of wet granulation or that of direct compression. With dry granulation it is often possible to compact the active ingredient with a minor addition of lubricant and disintegrating agent. Fillers that are used in dry granulation include Lactose, dextrose, sucrose, MCC, calcium sulphate, Sta-Rx ® etc.

2.15 **Recent advances in Granulation techniques**

- i. Steam Granulation
- ii. Melt granulation/thermoplastic granulation
- iii. Moisture activated dry granulation (MADG)
- iv. Moist granulation technique (MGT)
- v. Thermal adhesion granulation process (TAGP)
- vi. Foam granulation. (www.pharmainfo.net)

2.16 **Direct Compression**

It is referred to as a process by which the tablets are compressed directly from a powder blend of the active drug and suitable excipients. It is used mainly for crystalline chemicals having all the physical characteristics required for the formation of the tablets. It is the most preferred and economical tableting process since it requires only four steps as compared to wet granulation and dry granulation method.

The excipients consist of diluents, binders and disintegrants. For good tablets to be formed, the powder blend has to flow uniformly and form firm compacts. Direct compression vehicle should be free flowing, physiologically inert, tasteless and

colourless. Some drugs like aspirin require the addition of direct compressible diluents like microcrystalline cellulose, dibasic calcium phosphate.

2.16.1 Steps for Direct Compression

Direct compression involves comparatively few steps:

- i. Milling of drug and excipients
- ii. Mixing of drug and excipients
- iii. Tablet compression.

2.16.2 Direct Compression Excipients

Direct compression excipients mainly include diluents, binders and disintegrants. Generally, these are common materials that have been modified during the chemical manufacturing process, in such a way as to improve compressibility and flowability of the material. The physicochemical properties of the ingredients such as particle size, flowability and moisture content are critical in direct compression tableting. The success of direct compression formulation is highly dependent on functional behaviour excipients. (www.pharmainfo.net).

An ideal direct compression excipient should possess the following attributes:

- i. It should have good compressibility
- ii. It should possess good hardness after compression, that is, material should not possess any deformational properties; otherwise this may lead to capping and lamination of tablets
- iii. It should have good flowability
- iv. It should be physiologically inert
- v. It should be compatible with a wide range of API

- vi. It should be stable to various environmental conditions (air, moisture, heat, and so forth).
- vii. It should not show any physical or chemical change in its properties on aging
- viii. It should have high dilution potential, that is, should be able to incorporate high amount of API
- ix. It should be colourless, odourless and tasteless
- x. It should accept colourant uniformity
- xi. It should possess suitable organoleptic properties according to formulation type that is in case of chewable tablet, diluents should have suitable taste and flavour. For example mannitol produces cooling sensation in mouth and also sweet taste.
- xii. It should not interfere with bioavailability and biological activity of active ingredients
- xiii. It should be easily available and economical in cost

2.17 Merits of direct compression

- i. Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
- ii. The most important advantage of direct compression is economical process. Reduced processing times reduced labour cost, fewer manufacturing steps, and less number of equipment are required, less process validation, reduced consumption of power.

- iii. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API's
- iv. Particle size uniformity
- v. Prime particle dissolution; In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates, thus decreasing the surface area available for dissolution.
- vi. The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes are fewer.
- vii. Chemical stability problems for API and excipients are avoided
- viii. Provides stability against the effect of aging which affects the dissolution rates.

The variables faced in the processing of the granules can lead to significant tableting problems. Properties of granules formed can be affected by viscosity of granulating solution, the rate of addition of granulating solution, type of mixer used and duration of mixing, method and rate of dry and wet blending.

The above variables can change the density and the particle size of the resulting granules and may have a major influence on fill weight and compaction qualities. Drying can lead to unblending as soluble API migrates to the surface of the drying granules.

2.18 Demerits of direct compression

2.18.1 Excipients Related demerits

- i. Problems in the uniform distribution of low dose drugs
- ii. High dose drugs having bulk volume, poor compressibility and poor flowability are not suitable for direct compression. For example, Aluminum hydroxide, magnesium hydroxide
- iii. The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flowability
- iv. Many active ingredients are not compressible at all whether in crystalline or amorphous forms
- v. Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending
- vi. Non-uniform distribution of colour, especially in tablets with deep colours

2.18.2 Process Related demerits

- i. Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expands when the pressure of tablets is released, resulting in splits or layers in the tablet.
- ii. In some cases the process requires greater sophistication in blending and compression equipment.
- iv. Direct compression equipment is expensive.

2.19 **Essential excipients for direct Compression**

- i. Diluents
- ii. Binders

This method is superior to those methods employing liquids since it does not require equipment and handling expenses required in wet and dry granulation. Research in direct compression involves the production of excipients which are directly compressible where they serve as filler-binder for poorly compressible drugs. This advancement has made it possible for thermolabile and moisture sensitive active ingredient to be compressed in to standard tablets. Hydrolysis of water soluble sensitive drugs can also be avoided (www.pharmainfo.net).

Table 2.1 STEPS IN PRODUCTION OF TABLETS BY WET, DRY GRANULATION AND DIRECT COMPRESSION. (file:///G:/Starch.html 2004)

WET GRANULATION	DRY GRANULATION	DIRECT COMPRESSION
Weighing	Weighing	Weighing
Mixing	Mixing	Mixing
Preparing binder solution	Preparing	Admixing disintegrant,
	Slug by pre compression	lubricant
Moistening	Dry screening	Compressing
Wet screening	Admixing disintegrant	
	Lubricant	
Drying	Compressing	
Dry mixing		
Admixing		
Disintegrant, lubricant		
Compressing		

To most pharmaceutical manufacturers, the direct compression method is cheaper, has lesser investment in equipment, space and manpower, lower operating cost, elimination of granulation process and variability in granulation. The tablets also disintegrate into primary particles rather than into granules.

2.20 Tablet Compression

Compression takes place when the appropriate volume of granules or materials in a die cavity is compressed between the upper and lower punch and are consolidated into a single solid mass and ejected from the die cavity as an intact

tablet. Process of compression is described in terms of relative volume and applied pressure. This may be expressed by Heckel equation in terms of relative density rather than volume.

2.21 Compressional Characteristics of Granules

Plastic materials deform by changing shape while there is very little permanent change in elastic material during compression. Although, tableting materials should be plastic, that is, capable of permanent deformation, they should also exhibit a degree of brittleness (fragmentation).

2.22 Tablet Properties

Conventional tablets generally should have a certain amount of hardness, resistance to friability, ability to withstand the rigor of mechanical shock encountered during their production, packing and transportation and handling prior to use. The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness.

The small and portable hardness tester was manufactured and introduced by Monsanto in the mid-1930s. It is now designated as either the Monsanto or Stokes hardness tester. The instrument measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. Hardness testing, which is now more appropriately called crushing strength determination is done during tablet production and is used to determine the need for pressure adjustment on tablet machine

If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications. If it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging

and shipping operations. The force required to break the tablet is measured in kilograms and a crushing strength of 4 kgF is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10 kgF. However, hypodermic and chewable tablets are usually much softer (3 kgF) and some sustained release tablets are much harder (10-20 kgF).

Tablet hardness has been associated with other tablet properties such as density and porosity. Hardness generally increases with normal storage of tablets and depends on the shape, chemical properties, binding agent and pressure applied during compression (Pharmmedia 2010).

The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

These tablet properties together with uniformity of weight, disintegration, and dissolution depends on tableting condition employed, or size and distribution of the granules and predominantly on the formulation process employed. Granules with best mechanical and physical characteristics will produce tablet with best pharmaceutical properties.

2.23 Tableting Machines

The powders or granules are converted to suitable compacts or tablets using tableting machines. The machines commonly used include:

- i. Single punch tableting machine
- ii. Rotary tableting machine
- iii. Multilayer tableting machine.

The rotary tableting machines are known by the number of stations present, a die and two punches make a station, the machine could be made up of 16, 32 and 50 stations making it suitable for large scale production.

2.24. Modifications on Tableting Machines

2.24.1 Compaction Simulator

These are tableting machines used to study the mode of deformation of the powder and their compressional behaviour. They could be single punch or multi stations. An advantage of compaction simulators includes.

- i. It can make single tablets in the manner of any current tableting machine.
- ii. It can be used to investigate scale-up problems with a particular machine.
- iii. Small quantities of materials can be utilized.
- iv. It can be used to compress tablets containing radioactive marked substances for tracer substances.

CHAPTER THREE

MATERIALS AND METHODS

3.1 Materials

3.1.1 Chemicals and reagents

- i. A 7595 α -amylase enzyme (Sigma Aldrich laborchemikalien GmbH, Germany)
- ii. Hydrochloric acid (Sigma Aldrich laborchemikalien GmbH, Germany)
- iii. Chloroquine powder (May and Baker Ltd, Dagenham, England)
- iv. Sodium Hydroxide (May and Baker Ltd, Dagenham, England)
- v. Ethanol (Park Scientific Ltd, Northampton, U.K)
- vi. Magnesium Stearate (Hopkins and Williams, U.K.)
- Viii Iodine solution (BDH, Poole, England)
- ix Xylene (May and Baker Ltd, Lagos, Nigeria).

3.2 Methods

3.2.1 Collection and Identification of Cassava Tuber

The freshly harvested cassava tubers were collected and identified by the Institute of Agricultural Research, Ahmadu Bello University, Zaria and a voucher no 2347 was obtained for references.

3.2.1.1 Extraction of Cassava Starch:

Extraction of cassava starch was carried out using method described by Linus, (1995). The freshly harvested tubers of cassava were washed with distilled water, peeled, weighed and cut into smaller pieces, washed again and then grated. The grates were reduced into fine pulp using a blender. Ten litres (10 L) of distilled

water was poured into the pulp, thoroughly mixed and passed through a Calico cloth sieve with the addition of more water to ensure good recovery of starch.

The starch was allowed to settle very well and the excess water was decanted, the residual starch was washed several times with 0.1N Sodium hydroxide to neutralize the slightly acidic nature of the starch. Excess alkali was removed by washing several times with distilled water. A suspension of the starch in distilled water was centrifuged and the supernatant fluid decanted. The brown (protein) layer was scraped off and the tightly packed starch was collected and spread on a tray to dry for 24 h, after which it was dried in the oven (Gallenkamp BS size 3, England) at 40 °C for 6 h. The dried starch was size reduced and passed through 180µm sieve size. The percentage yield was calculated from the initial and final weights obtained.

3.2.1.2 Preparation of Enzyme - hydrolyzed Starch (EHS)

The production of Enzyme-hydrolyzed starch (EHS) was carried out using the method described by the World Intellectual property Organization (WIPO, 1997). An aqueous suspension of starch (40 % w/v) was brought into a double-walled reaction vessel under optimum pH and temperature. The reaction was allowed to proceed for 1, 2,3,4,5 and 6 h. with the dosed enzyme (0.1 ml of α -amylase BAN 240L) and constant stirring.

Afterwards, the action of the enzyme was terminated by lowering the pH to 2.5 with 0.1N HCl. The reaction medium was subsequently neutralized by raising the pH to 7 using 0.1N NaOH. The resulting product was separated from the reaction medium after settling down. It was washed several times with distilled

water and then dehydrated with 100 ml of ethanol (95 % v/v). The dehydrated product was air dried and powdered after decanting the ethanol. The percentage yield was calculated from the initial and final weights obtained

3.3 **Physicochemical Tests on the Starch**

3.3.1 **Organoleptic properties** such as taste, colour, odour and texture were determined

3.3.2 **Test for starch.** This was carried out using the method described in (B.P. 2002): one gram of the starch was suspended in 50 ml of distilled water. It was boiled for 1 min and cooled. To 1ml of the mucilage, 0.05 ml of iodine solution was added. The change in colour was observed.

3.3.3 **Ash Content:** This was determined by the measurement of the residue left after the combustion in oven (Gallenkamp, Philip Harris Ltd., England) of two gram of starch in a silica dish at 450 °C and the percentage of ash was calculated with reference to the starch.

3.3.4 **pH Determination:** This was determined by shaking 1 g of the powdered material with 100 ml of distilled water for 5 min and the pH of the supernatant liquid determined using a pH meter.

3.3.5 **Solubility:** Two gram of each sample was dispersed in 10 ml of cold water, hot water, acetone, ethanol and chloroform and left overnight. Five ml of the clear supernatant solution was taken and heated to dryness over a water bath. The weight of the dried residue with reference to the volume of the solution was determined accordingly as the percentage solubility of the starch in the solvent.

3.3.6 **Microscopy:** A pinch of the starch was mounted on a slide in glycerol, the size of the starch grain was measured using the calibrated eyepiece micrometer.

3.3.7 **Percentage Moisture Loss:** Five gram of the starch was weighed and dried to constant weight at a temperature of 105 °C. The loss in weight was determined and expressed as percentage moisture content.

3.3.8 **Bulk and tapped densities:** Fifty gram of the powder was poured into a 50 ml measuring cylinder and the volume noted. This was gently tapped on a flat surface from a height of 2.5 cm three times at 2 s intervals for 5, 25 and 50 taps and the final volume was noted. The bulk and tapped densities were calculated as the ratio of weight to volume

The data generated were used in computing the Carr's index (CI) and Hausner's ratio using the equation below.

$$B.D = \text{Weight of powder} / \text{initial volume} \text{-----} (4)$$

$$T.D = \text{Weight of powder} / \text{Final volume} \text{-----} (5)$$

$$C.I = T.D - B.D / T.D \times 100 \% \text{-----} (6)$$

$$H.R = T.D / B.D \text{-----} (7)$$

H.R = Hausner Ratio

T.D = Tapped Density

B.D = Bulk Density

C.I = Carr's Index

3.3.9 **Moisture Sorption Capacity:**

Two gram of the starch was accurately weighed and evenly distributed over the surface of a 70 mm tarred Petri dish. The sample was placed in a large desiccator containing distilled water at its base at room temperature in order to achieve 100 % Relative Humidity and the weight gained by the exposed sample at

the end of a five day period was recorded and the amount of water uptake was calculated from weight difference.

3.3.10 Particle Density

A method described by Odeku *et al* (2005) was adopted. The particle density was determined with a pycnometer bottle using xylene as the displacement fluid. An empty 50 ml pycnometer bottle was weighed (W), filled with xylene and the excess wiped off. The filled bottle was weighed a second time (W_1) and the differences between W_1 and W obtained as W_2 . A 2 g quantity of the powder was weighed (W_3) and transferred into the pycnometer bottle.

The excess solvent was wiped off and the bottle weighed again (W_4). The particle density, ρ_t (g/cm³), was then calculated from the equation given below:

$$\rho_t = (w_2 \times w_3) / 50 (w_3 - w_4 + w_2 + w) \text{ ----- (8)}$$

3.3.11 Powder Porosity

This was derived from the values of true and bulk densities when fitted into the equation below.

$$\varepsilon = 1 - 100 D_b / D_t \text{ (9)}$$

Where ε is the porosity,

D_b is the bulk density and

D_t is the true density.

3.3.12 Swelling Power

The swelling capacity of the powder was estimated by a method described by Iwuagwu and Onyekweli (2002). The tapped volume occupied by 5 g of the powder, V_x , was noted. The powder was then dispersed in 85 ml of water and the

volume made up to 100 ml with more water. After 24 h of standing, the volume of the sediment, V_v , was estimated. The swelling capacity was computed as follows:

$$V_v / V_x \dots\dots\dots (10)$$

3.3.13 Hydration Capacity

The method of Kornblum and Stoopak (1973) was used. A 1 g sample was placed in each of four 15 ml plastic centrifuge tubes to which 10 ml distilled water was added and then stoppered. The contents were mixed on a vortex mixer for 2 minutes. The mixture was allowed to stand for 10 minutes and then centrifuged at 1000 rpm for 10 minutes on a bench centrifuge.

The supernatant was carefully poured out and the sediment weighed. The hydration capacity was determined as the ratio of sediment weight to the dry sample weight.

3.4 Formulation Studies

The Enzyme- hydrolyzed starch was used to formulate Chloroquine tablets using the wet granulation and direct compression method.

3.4.1 Preparation of Granules

The wet granulation method of massing and screening was used with cassava starch as binder. There was mixing of drug and excipients followed by preparation of binder solution and then mixing of binder solution with powder mixture to form a wet mass and this was passed through a suitable sieve 1.7mm mesh and then dried in a hot air oven at 60 °c for 1 h.

The dried granules were screened through 1.6 mm mesh and finally, the screened granules were mixed with disintegrants, glidant and lubricants.

Table 3.1 Tablet formula for Chloroquine Phosphate tablet formulations (wet granulation).

Material	Per tab (mg)	Batch (100)
Chloroquine	250	25 g
Disintegrant(MS)10% w/w	25	2.5 g
Binder*	QS	QS
Maize starch	7.8 % w/w	0.78 % w/w
Talc	2 % w/w	0.2 % w/w
Mag. Stearate	0.2 % w/w	0.02 % w/w
Total	310	31 g

KEY;

Binders*:

Native Cassava starch 2.5, 5.0, 7.5 and 10 % w/v

Enzyme -hydrolyzed starch 2.5, 5.0, 7.5 and 10 % w/v

Maize starch 2.5, 5.0, 7.5 and 10 % w/v

Polyvinyl pyrrolidone 2.5, 5.0, 7.5 and 10 % w/v

MS: Maize starch

**Table 3.2: Tablet Formula for Chloroquine Phosphate tablet formulations
(Direct compression).**

Materials	Batches				
	I	II	III	IV	V
Chloroquine (mg)	250	250	250	250	250
EHS	0.0	93.44	186.88	280.30	373.76
Avicel. Binder (mg)	373.76	280.30	186.88	93.44	0.0
Mag. Stearate (0.2 % w/w)	1.25	1.25	1.25	1.25	1.25
Total tablet weight (mg)	625	625	625	625	625

KEY:

EHS ; Enzyme – hydrolyzed starch

I EHS : Avicel (MCC) 0 : 100

II EHS : Avicel (MCC) 25 : 75

III EHS : Avicel (MCC) 50 : 50

IV EHS : Avicel (MCC) 75 : 25

V EHS : Avicel (MCC) 100 : 0

3.4.2 Physicochemical Tests on Granules

The following physicochemical tests were carried out on the granules. They include;

- i. Bulk and tapped densities
- ii. Particle size analysis
- iii. Percentage moisture loss
- iv. Angle of repose
- v. Flow rate

3.4.3 Bulk and Tapped Densities

Thirty g of each batch was poured into a 100 ml calibrated glass cylinder through a short stemmed glass funnel and the volume occupied by the granules was read and used to calculate the bulk density (BD). The cylinder was then tapped 10, 20, 30 times until a constant weight was obtained. The reading of the final volume was used to calculate the tapped density (TD). Both densities were expressed in g/ml and the mean of two readings was recorded. Carr's index (C.I) and Hausner ratio (H.R) were calculated using these equations.

$$C.I = (TD - BD / TD) \times 100$$

$$H.R = TD / BD$$

3.4.4 Particle Size Analysis

This was carried out using a light microscope with a micrometer. 0.5 grams of the granules were dispersed in a drop of glycerol on a microscope and covered with a slip. The particle shape was determined at 400 x magnification.

Using the sieve analysis method, Twenty gram was placed on a nest of sieves containing sieves arranged in descending order (500, 250, 150, 90 and 75 μ m) and

the shaker vibrated for 15 min. The weight of starch retained on each sieve was taken and percentage cumulative weight oversize was plotted against particle size.

3.4.5 **Determination of Flow Rate**

Fifty grams of the granules was allowed to flow through the orifice of the flowability tester. The time taken for the granules to pass through the orifice was noted and the flow rate was calculated.

3.4.6 **Determination of Angle of Repose**

Fifty g of granules was allowed to flow through a funnel to form a heap on a clean flat surface from a distance of 10 cm from the flat base to the tip of the funnel. The angle of repose (Θ) was calculated from tangent of the base radius (r) and height of the heap (h).

$$\tan \Theta = h/r \text{ ----- (11)}$$

3.5 **Tablet Production**

Two methods were used for tablet production and they are wet granulation and direct compression. In wet granulation method of compaction, the granules were poured in a Tumble mixer after which extra granular excipients like 2 % dried talc, 0.2 % w/w magnesium stearate and 7.8 %w/w maize starch BP were added and mixed for 5 min. The granules were compressed at 7.0 metric tons using 12.0 mm normal concave-faced punches on a single punch tableting machine (Type AR 400, Erweka Apparatebau. G. M. B. H Heusentamm, Germany).

For Direct compression, the formula in Table 3.2 was used to prepare 100 tablets per batch. The batches contain different proportions of Enzyme-hydrolyzed starch and Avicel^R in the following proportions; 0:100, 25:75, 50:50, 75:25, and 100:0, and the batches were labeled accordingly. Binary mixture of EHS and

Avicel^R were prepared by weighing EHS and Avicel^R using a weighing balance (Mettler balance, Switzerland). They were transferred into a mortar and mixed with a pestle. Twenty five gram of chloroquine phosphate powder was weighed and transferred to the mortar, the mixture was well mixed with pestle after which it was lubricated with 125 mg magnesium stearate and it was compressed directly using a single punch tabletting machine.

3.5.1 **Tablet Properties (Quality Control tests)**

3.5.1.1 **Uniformity of Weight**

Twenty tablets were weighed individual and collectively from each batch using digital electronic balance and the mean was calculated with the percentage deviations determined.

3.5.1.2 **Diameter Measurement**

The diameter of tablet was measured using the micrometer screw gauge 24 h after the tablet has been compressed. Diameters of five batches were measured and the mean calculated.

3.5.1.3 **Thickness and Porosity:**

The thickness of the tablets was measured using a sliding Vernier caliper (Moore and Wright Sheffield, England).

Tablet Porosity, T_p was calculated using the following equation.

$$T_p = 1 - \frac{m}{\rho_t v} \times 100 \text{-----} (13)$$

ρ_t = True density in g/ml

m = Weight

v = volume of tablet which can be calculated from the formula

$$v = \pi r^2 h$$

h = Height

3.5.1.4 **Crushing Strength**

Five tablets were randomly selected from each batch, Monsanto hardness tester (Pharma tester PTB 301) was used to measure the crushing strength. Tablet was placed between the spindle and anvil of the tester and the calibrated length was adjusted to zero. The knob was screwed gradually and gently to apply a diametric compression force on the tablet and the pressure was recorded in kgf units. A mean value of the crushing strength was calculated for each batch.

3.5.1.5 **Friability Test**

Ten tablets were dusted, weighed together and subjected to abrasion test in a Roche friabilator (Type TA3R, Erweka Apparatebau. GmbH Heusenstamm, and Germany) operated at 25 rpm for 4 min. The tablets were then dusted properly and weighed again collectively. The difference in weight was determined and expressed as percentage friability value.

3.5.1.6 **Density of Tablets**

Density of tablets at corresponding pressure loads were used to evaluate compressibility. Tablet density was obtained from the weight of compact and its volume calculated as follows:

$$D = M / \rho_t v \text{ ----- (14)}$$

Where D = Relative density

M = Weight

v = Volume

ρ_t = true density of the granules or particle density

3.5.1.7 Disintegration Time Studies

The B.P (2003) method was used. Six tablets were randomly selected from each batch and were placed one in each of the cylindrical tubes of the apparatus. The water in the apparatus was thermostatically maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The time taken for each tablet to break into small particles and pass through the mesh was recorded. The Mean disintegration time was calculated for each batch.

3.5.1.8 Dissolution Studies

(a) Calibration curve for chloroquine

A 0.1 mg/ml stock solution of chloroquine was prepared by dissolving 100 mg of chloroquine in 1000 ml of 0.01N HCl. Serial dilutions were performed to yield solutions of concentration ranging from 3.13 – 100 $\mu\text{g/ml}$. The absorbance of each concentration was taken at 277 nm and plotted against the various concentrations to obtain the calibration curve for chloroquine. The linear regression equation for the graph was resolved from the plot and used to calculate the amount of drug released with time during dissolution studies.

The dissolution rate of the tablets was determined using an Erweka dissolution apparatus (Type DT, Erweka Apparatebau. GmbH Heusenstamm, and Germany). The dissolution medium was 1000 ml of 0.1N HCL for the chloroquine tablet and it was thermostatically maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The revolution of the basket containing the test tablet was 100 rpm. Ten milliliters of the sample were withdrawn from a position half way between the surface of the dissolution medium and the top of the rotating basket at 5 min interval for one h.

Each volume of sample withdrawn was replaced with an equivalent volume of dissolution medium maintained at the same temperature. A tenfold (1:9) dilution with the dissolution medium was done for each sample withdrawn before absorbance of the samples were read at 277 nm using a Helios Zeta UV/VIS spectrophotometer (Thermo Fisher Scientific inc. 19 Mercers Row, Cambridge UK). The percentage drug released was plotted against time to generate a dissolution curve.

3.6 Tablet tensile strength:

This is the stress needed to fracture a tablet by diametrical compression. It is given by the expression below (Fell and Newton, 1970):

$$TS = \frac{2P}{\pi Dt} \text{-----} (15)$$

P is the load that causes tensile failure of a tablet.

D is the diameter and t = thickness.

The fracture load of five tablets was determined individually with the Monsanto hardness tester, following Brook and Marshal (1968). The mean values of the fracture load were used to calculate the TS values for the various tablet formulations (Emmanuel, 2010).

CHAPTER FOUR

4.1 RESULTS

Table 4.1: Results of Organoleptic investigations on the starches

Properties	NCS	EHS	MS
Odour	odourless	odourless	odourless
Colour	white	white	white
Taste	tasteless	tasteless	tasteless
Texture	smooth	smooth	smooth

Table 4.2: Results of some micromeritics properties of the starches.

Properties	NCS	EHS	MS
Ash value (%)	1.00	1.00	4.10
Flow rate (g/s)	1.92	1.62	1.50
Bulk density (g/cm ³)	0.61+1.24	0.47±0.08	0.45±0.51
Tapped density (g/cm)	0.72	0.52	0.62
Hausner's ratio	1.20	1.08	1.17
Carr's index (%)	16.67	9.62	10.9
Particle density (g/cm ³)	1.63	1.49	1.47
Particle size range (µm)	2 – 10	2 – 11.80	2 – 12.70
Powder porosity (%)	27	35	63.5

key: NCS = Native cassava starch. EHS = Enzyme Hydrolyzed Starch

MS = Maize Starch

Table 4.3: Results of some physicochemical properties of the starches.

Properties	NCS	EHS	MS
Percentage yield (%)	20	85	
pH	6.25	6.96	6.50
Iodine test	blue-black	blue-black	blue-black
Loss on drying (% w/w)	0.50	1	4
Particle size range (µm)	2 - 10	2 – 11.8	2 – 12.70
Particle shape	spherical	spherical	spherical
Angle of repose (⁰)	33.3	26.6	26.0
Swelling power	1.45	1.23	1.20
Moisture sorption capacity	11	8	10.5
Moisture loss (%)	0.5	1	5.6
Hydration capacity	1.29	0.9	1.32
Solubility in cold water (% w/v)	0.02	0.02	0.02
Solubility in hot water (% w/v)	0.20	0.20	0.20

key: NCS = Native cassava starch. EHS = Enzyme Hydrolyzed Starch

MS = Maize Starch

The results of flow rate and angle of repose are presented in Table 4.2. The highest angle of repose was obtained with NCS (33.3 °); that of EHS was smaller (26.6 °). The results obtained indicated that NCS has poor flow properties. Bulk and tapped density values are also presented in Table 4.2. Carr's index and Hausner's ratio are calculated from the values obtained from bulk and tapped densities for each material and these values confirmed that NCS has poor flowability. Native Cassava starch has Carr's index of 16.67 % and Hausner's ratio of 1.2, while EHS has Carr's index of 9.62 % and Hausner's ratio of 1.08. MS and EHS exhibited good flow property. NCS has higher particle density of 1.63 compared to that of EHS of 1.49 and MS 1.47. Powder porosity ranged from 27 % for NCS to 35 % for EHS. The average diameter of particle size for NCS is 79.77 μm while that of EHS is 197.2 μm .

4.2 Microscopy

The photomicrographs of NCS, EHS and MS B.P. are shown in Plate 4.1, 4.2 and 4.3 respectively.

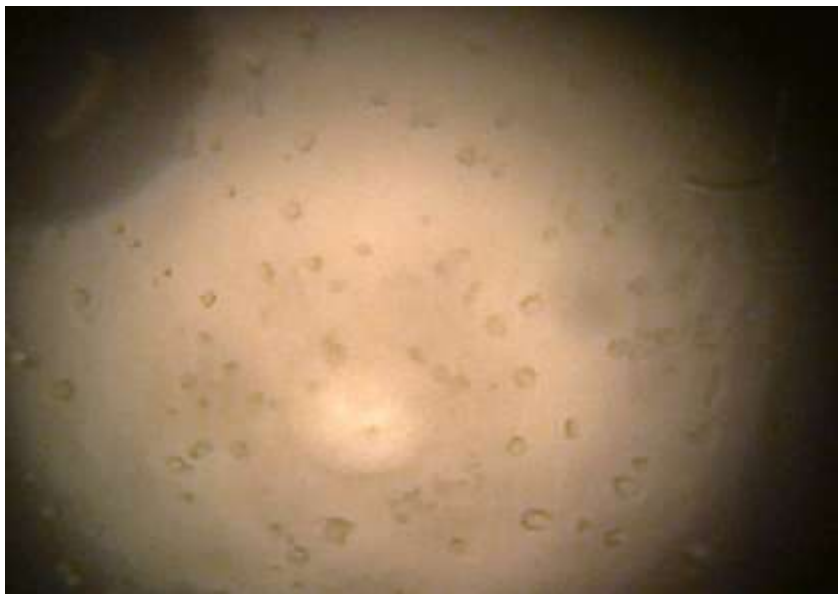


Plate 4.1 Photomicrograph of Native cassava starch
(Mag. X 400)

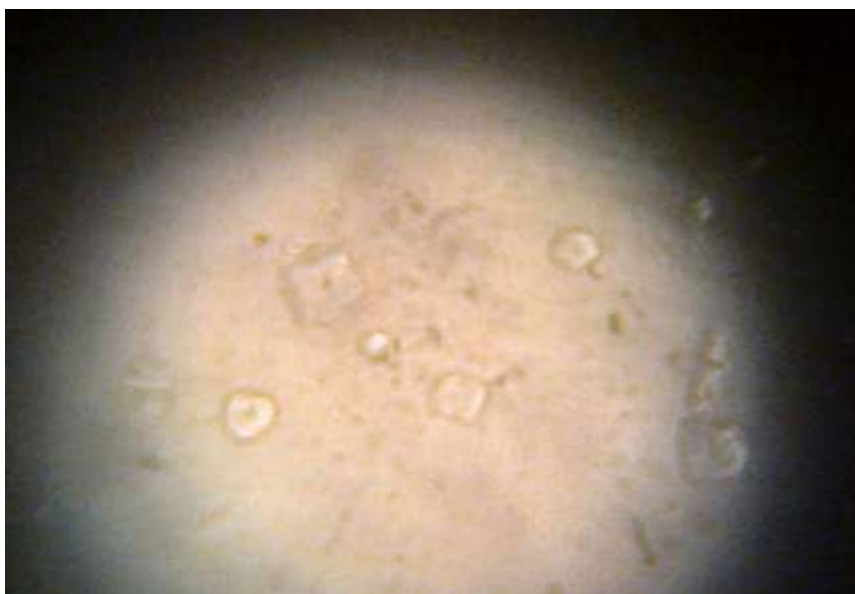


Plate 4.2 Photomicrograph of Enzyme-hydrolyzed starch
(Mag X 400)

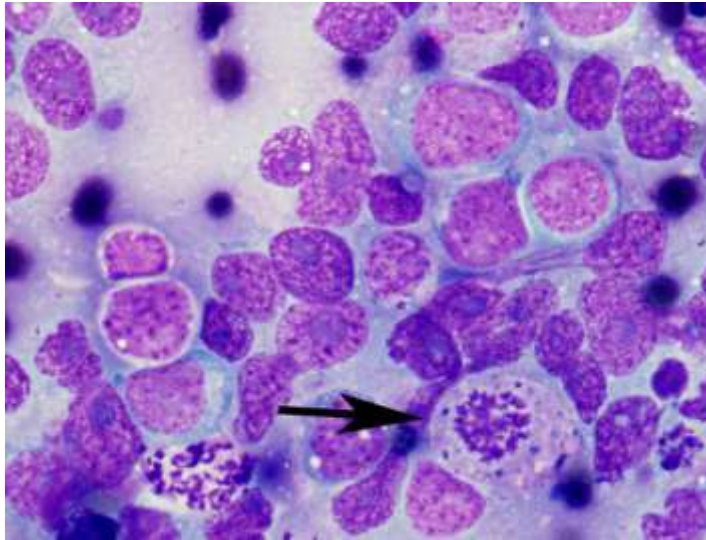


Plate 4.3 Photomicrograph of Maize starch B.P.
(Mag. X 400)

It was observed from the results obtained that all the starches are spherical in shape

Table 4.4 Results of the Dilution Potential of Tablets containing Graded portions of EHS, MCC and Chloroquine phosphate.

Binary mix ratio	EHS		MCC	
	CS (Kgf)	FR (%)	CS (Kgf)	FR (%)
90:10	9.2	0.83	12.9	0.34
80:20	9.0	0.90	12.6	0.36
70:30	8.5	0.95	12.5	0.40
60:40	8.4	1.02	12.1	0.45
50:50	8.2	1.08	11.2	0.52
40:60	7.5	1.10	10.1	0.70
30:70	7.0	1.12	9.3	0.80
20:80	6.0	1.20	8.2	0.88
10:90	5.0	1.30	6.5	0.98

90:10 = 90 % filler binder + 10 % drug

CS = Crushing strength. FR = Friability.

EHS = Enzyme – hydrolyzed starch

MCC = Microcrystalline cellulose

The results obtained for dilution potential are showed in Table 4.4 respectively. It contains the mechanical properties of tablets containing graded portion of Enzyme – hydrolyzed Starch (EHS), Microcrystalline Cellulose (MCC) and Chloroquine phosphate powder (CQ) and it can be observed from the tablets obtained from the formulation containing EHS: CQ that the crushing strength decreases as the proportion of EHS decreases and the friability also increases. Comparing the results obtained with EHS : CQ with that results obtained from the

MCC : CQ combination, it was observed that more compact tablets were produced with higher crushing strength and lower friability than EHS: CQ combinations.

4.3 Particle size analysis

The result and graph of particle size analysis of native cassava starch and Enzyme - hydrolyzed Starch and Maize starch BP using sieve analysis is presented in Appendix A.1.3 and Figure 4.1.

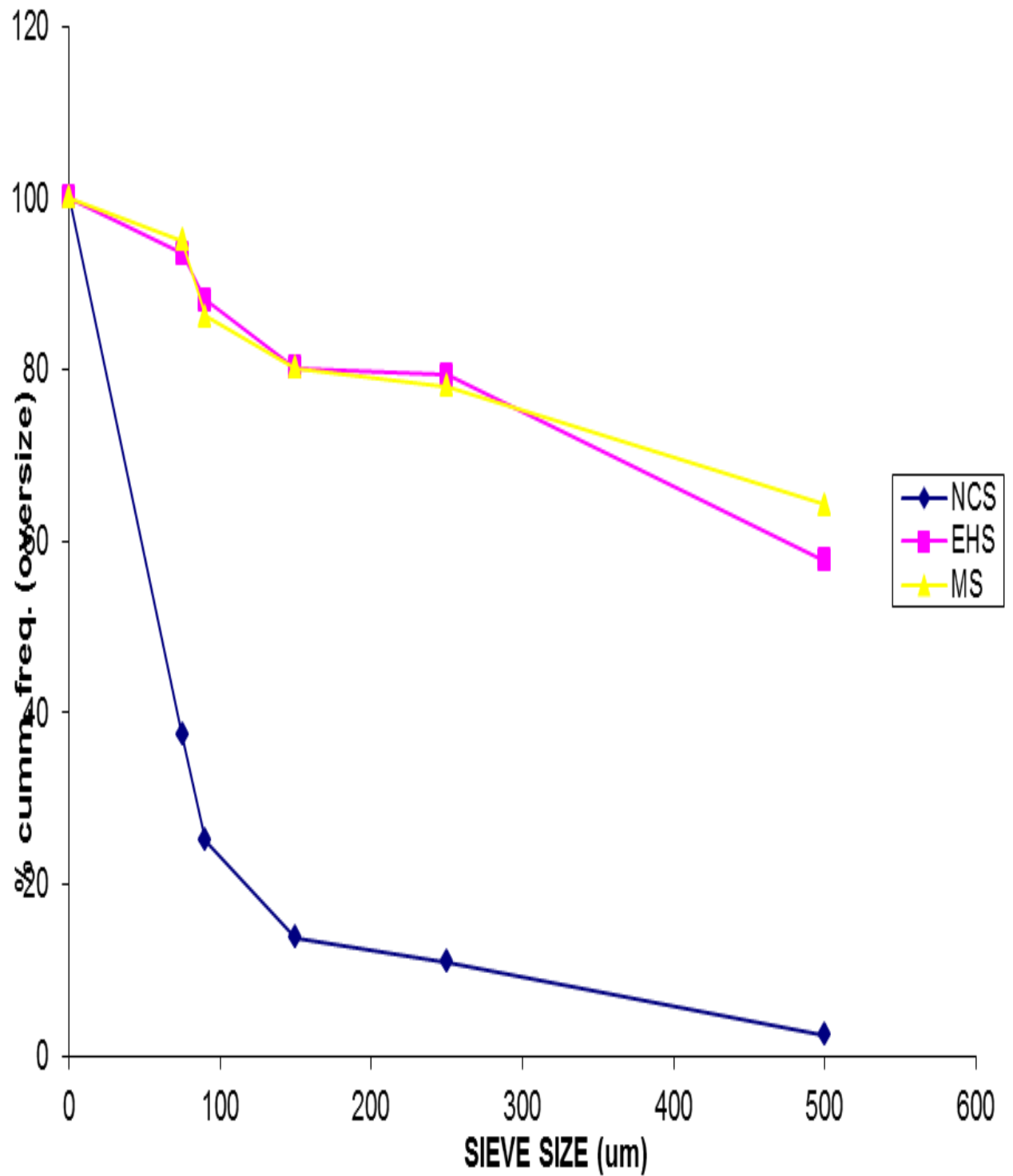


Figure 4.1: Graph of Percentage Cumulative Frequency oversize versus Sieve size (μm) for NCS, MS, and EHS using Sieve method.

MS and EHS contain larger particles which were mostly retained on the 500 μm sieve size, this may be due to increase in the formation of bond between Chloroquine Phosphate powder and other excipients and increase binder concentration. Particles of NCS were mostly retained at the lower sized s

4.4 Physical Properties of Chloroquine Granules

The effects of binder concentration on some of the physical properties of the granules produced by wet granulation are shown in Table 4.6 through the results of flow rate, sieve analysis, bulk and tapped densities, Carr's index, Hausner ratio, angle of repose and percentage moisture loss.

4.5 Effects of various binder concentrations on granules

Table 4.5: Effects of binder concentrations on the physical properties of the granules

	Bulk Density (g/cm³)	Tapped Density (g/cm³)	C.I (%)	H . R	Flow rate (g/s)	Angle of repose (°)	Moisture loss (%w/w)
2.5 % w/v							
NCS	0.53	0.54	1.85	1.02	3.73	21.8	1.0
EHS	0.50	0.53	3.85	1.04	3.33	21.8	0.5
PVP	0.53	0.53	0.00	1.50	3.58	16.7	1.5
MS	0.59	0.61	1.64	1.03	4.39	16.7	0.5
5.0 % w/v							
NCS	0.50	0.52	5.66	1.06	3.47	21.8	1.5
EHS	0.48	0.51	5.88	1.06	3.33	16.7	1.0
PVP	0.53	0.54	1.04	0.90	3.33	21.8	1.0
MS	0.50	0.53	5.66	1.06	3.36	21.8	0.0
7.5 % w/v							
NCS	0.54	0.57	5.26	1.06	3.33	21.8	1.5
EHS	0.48	0.50	4.00	1.04	2.91	21.8	0.0
PVP	0.43	0.48	0.06	1.07	3.16	16.7	0.5
MS	0.50	0.53	5.66	1.06	3.73	21.8	1.0
10 % w/v							
NCS	0.50	0.53	5.66	1.06	3.42	21.8	0.5
EHS	0.48	0.48	0.00	1.00	3.14	16.7	3.5
PVP	0.50	0.53	6.25	1.06	3.85	16.7	0.5
MS	0.45	0.48	0.06	1.07	3.16	16.7	0.5

KEYS;

C.I = Carr's index H.R = Hausner Ratio

It can be observed from the results obtained in Table 4.5 that there were reduction in the values obtained for bulk and tapped density as the concentrations of the binders increases and this could be as a result of increase in the cohesive bonds between the granules. There was also reduction in the flow rate for all the batches as the concentration of the binders increases, this could be as a result of the lubricant added thereby increasing its flowability.

4.6 Evaluation of Tablets properties produced by Wet Granulation

The properties of Chloroquine tablet produced by wet granulation using different binder concentrations are shown in Table 4.6.

Table 4.6. Properties of Tablets produced by Wet Granulation

Binder conc.	Mean weight (mg) \pm SEM	Thickness (mm)	Diameter (mm)	CS (kgf)	TS (MN/m ²)	FR (%)	DT (min)	CS-FR	CS-FR/DT
<u>2.5</u> %w/v									
NCS	312 \pm 1.79	2.78	10.61	6.6	0.14	0.94	2.8	5.66	2.02
EHS	310 \pm 2.77	2.54	10.61	6.8	0.16	0.90	3.0	5.90	1.96
PVP	315 \pm 1.80	2.78	10.55	8.3	0.18	0.74	3.9	7.56	1.94
MS	309 \pm 1.76	2.62	10.59	5.5	0.13	1.10	1.5	4.40	2.93
<u>5.0</u> %w/v									
NCS	305 \pm 2.78	2.76	10.60	6.8	0.15	0.89	3.1	5.91	1.91
EHS	305 \pm 2.55	2.54	10.57	7.2	0.17	0.80	3.3	6.40	1.94
PVP	300 \pm 2.01	2.72	10.58	8.6	0.19	0.72	4.2	7.88	1.88
MS	307 \pm 1.90	2.75	10.52	5.8	0.13	0.98	1.8	4.82	2.68
<u>7.5</u> %w/v									
NCS	308 \pm 1.98	2.55	10.20	7.5	0.18	0.78	3.3	6.72	2.04
EHS	305 \pm 3.05	2.48	10.65	8.0	0.19	0.76	3.6	7.24	2.01
PVP	320 \pm 4.23	2.88	10.63	9.3	0.19	0.68	4.9	8.62	1.76
MS	305 \pm 2.32	2.49	10.61	6.2	0.15	0.92	2.2	5.28	2.40
<u>10</u> % w/v									
NCS	312 \pm 1.85	2.68	10.67	8.0	0.18	0.79	3.7	7.21	1.95
EHS	308 \pm 3.25	2.82	10.60	8.6	0.18	0.72	4.4	7.88	1.79
PVP	305 \pm 3.95	2.68	10.60	9.5	0.23	0.66	5.0	8.84	1.77
MS	318 \pm 3.80	2.65	10.64	6.2	0.14	0.91	2.4	5.29	2.20

Key:

CS = Crushing Strength FR = Friability DT = Disintegration Time

From the results obtained in Table 4.5, it can be observed that as the binder concentrations increases the crushing and tensile strength increases, this could be as a result of increase in bonds formed between granules which leads to the production of stronger tablets. It can also be observed that as the binder concentrations increases, the friability decreases, this could be as a result of formation of stronger bonds which conferred resistance to tablet fracture and abrasion.

There was increase in the disintegration time as the binder concentration increases although all the batches disintegrate within the specified 15 min. The disintegration time, tensile strength and crushing strength are in this order of binders PVP > EHS > NCS > MS.

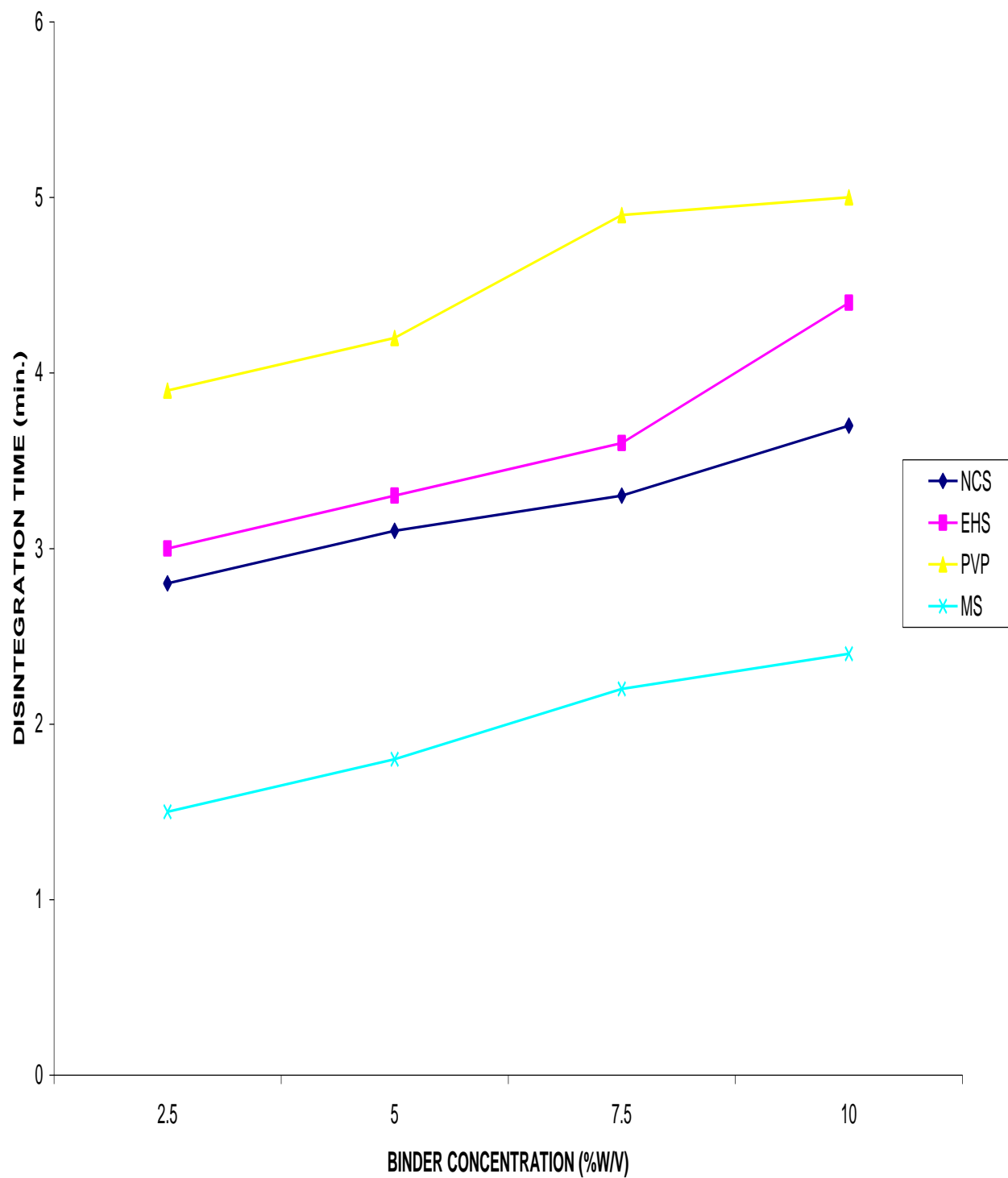


Figure 4.2: Graph of Disintegration time (min) versus Binder Concentration (%w/v) of Chloroquine phosphate Tablets produced by Wet Granulation Method.

The disintegration time increased with increase in the binder concentration at all levels for all binder types. Chloroquine tablets containing PVP as binder had the highest DT while that containing MS as binder had the lowest DT at all binder concentrations.

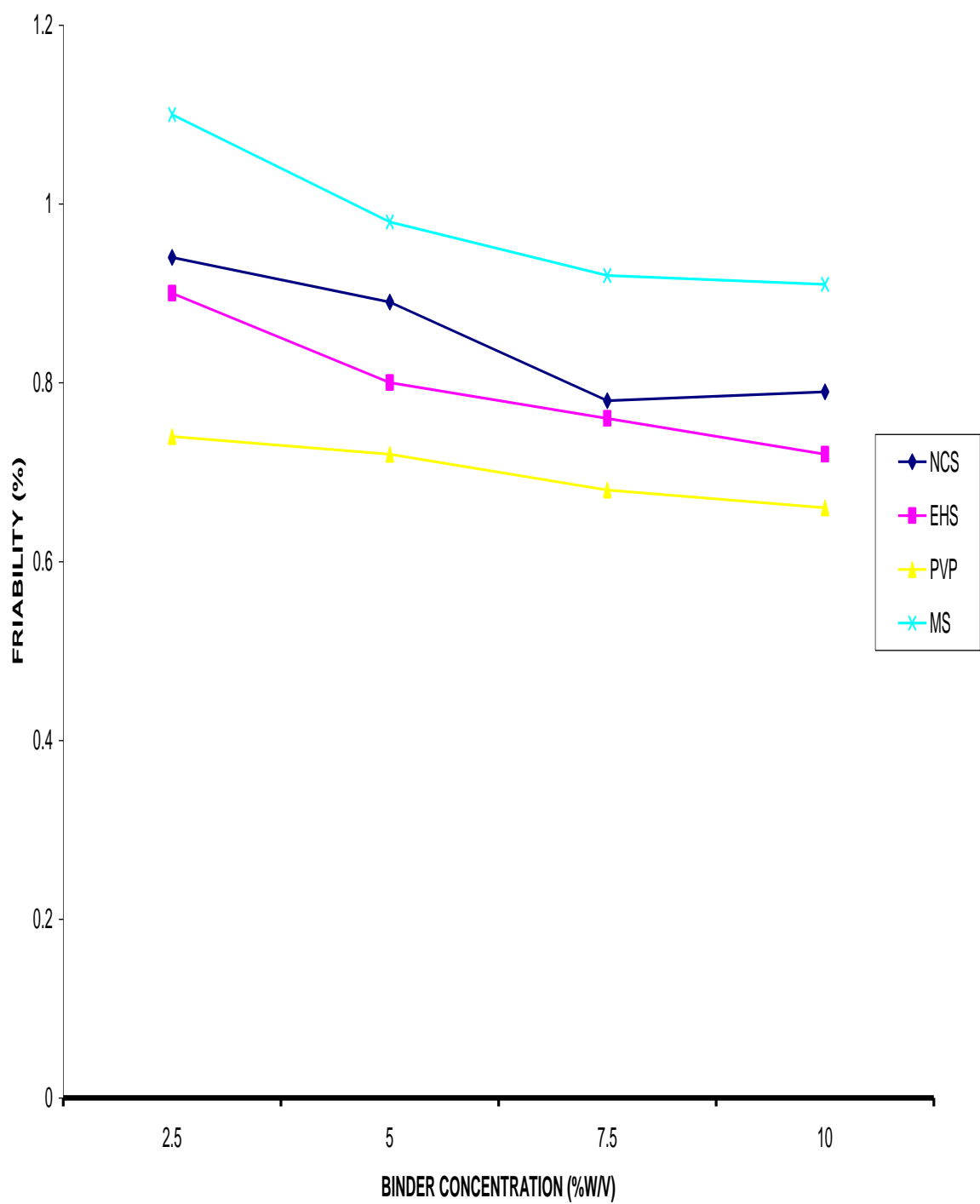


Figure 4.3: Graph of Friability (%) versus Binder Concentration (% w/v) of Chloroquine phosphate Tablets produced by Wet Granulation Method

As the binder concentration increases there was decrease in friability for all the formulations. Chloroquine tablets containing PVP as binder have the lowest friability while that containing MS has the highest. The friability of chloroquine tablets containing EHS is lower than that of NCS at all concentrations of binders. The 7.5 % w/v is the minimum binder concentration at which all the tablets passed friability tests.

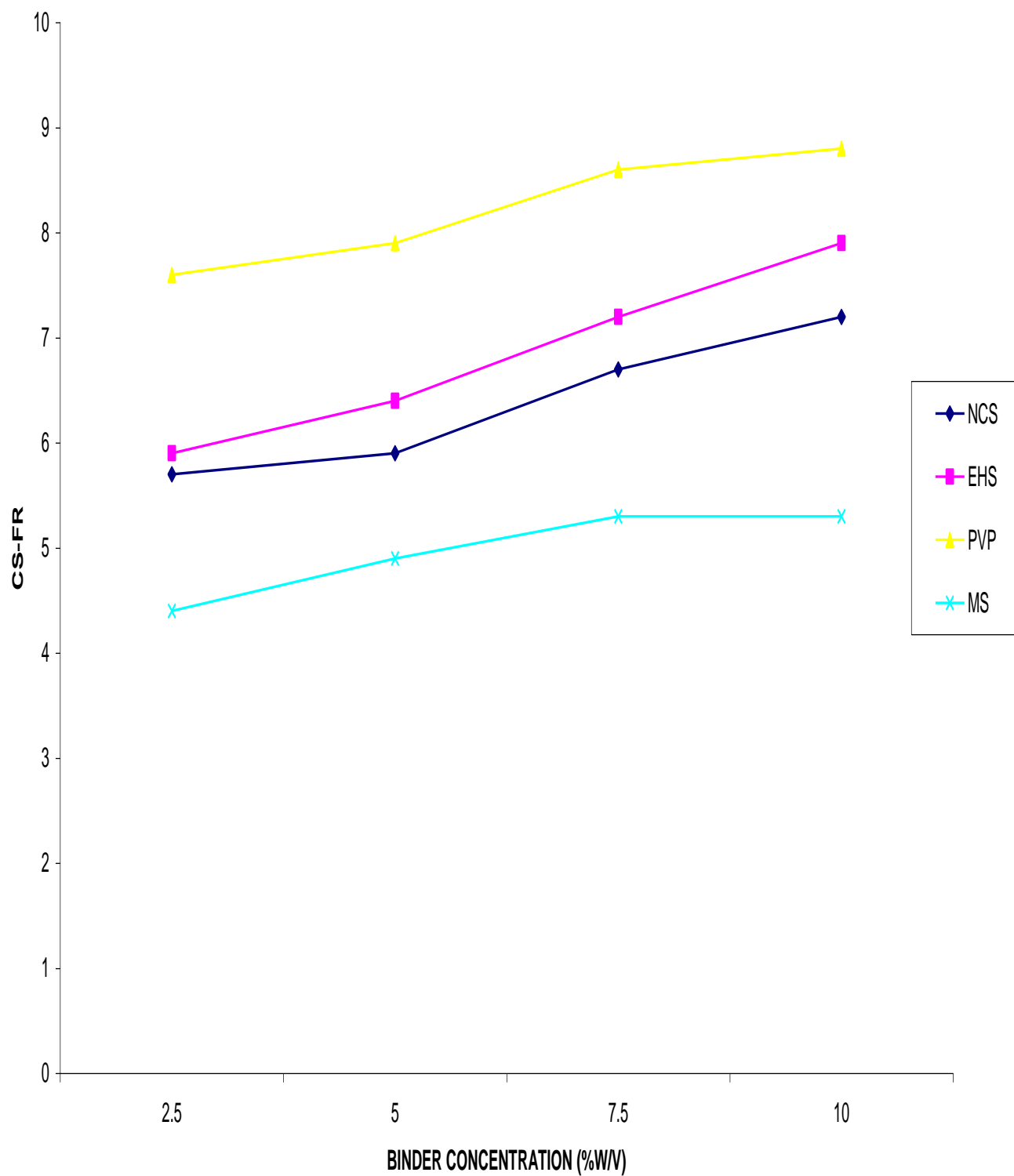


Figure 4.4: Graph of Crushing strength - Friability index versus Binder Concentration (% w/v) of Chloroquine phosphate Tablest produced by Wet Granulation Method

The CS-FR index increased with increase in binder concentration for all binder types. Maize starch B.P. has the lowest value while PVP had the highest CS-FR index at all concentrations.

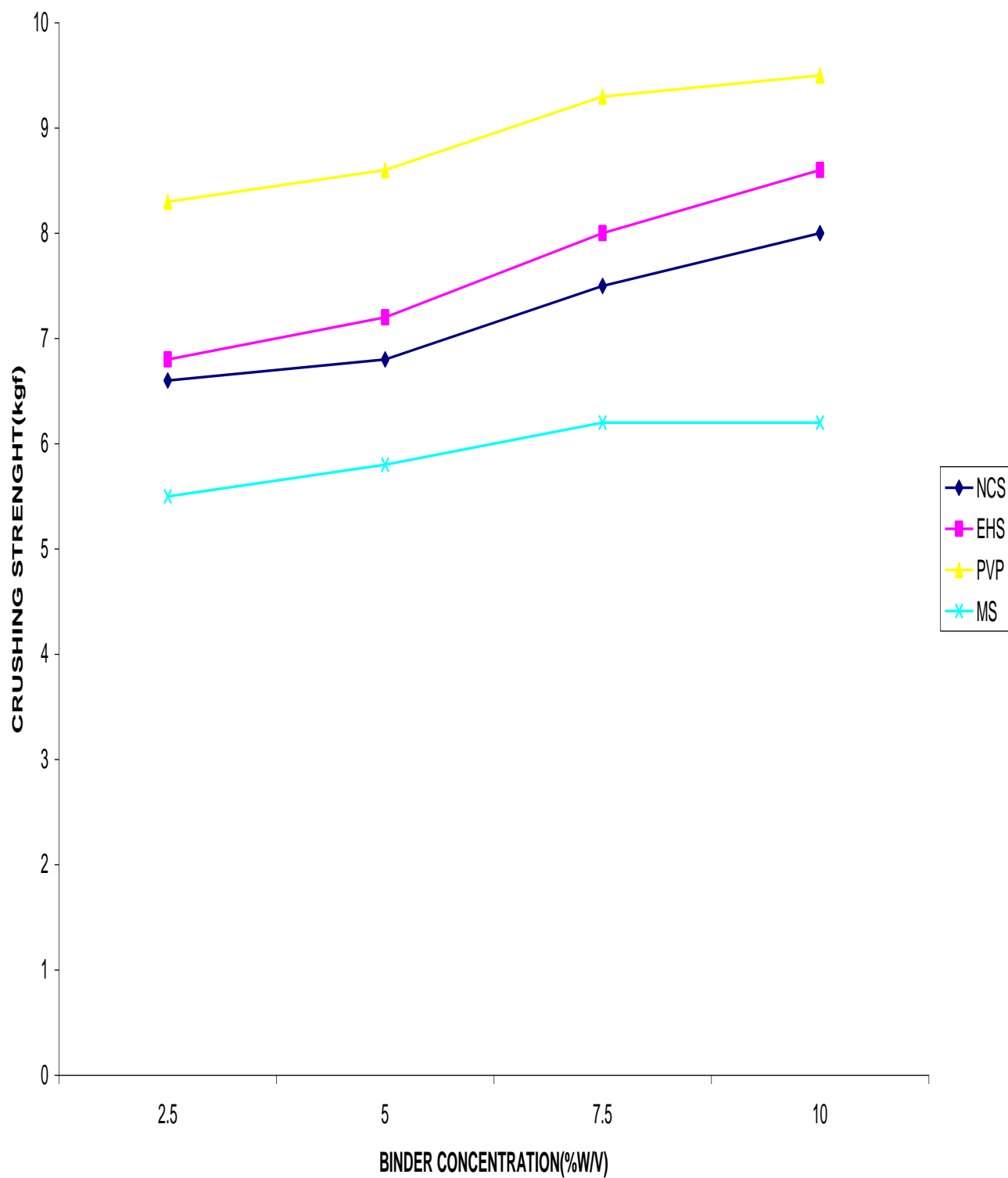


Figure 4.5: Graph of Crushing Strength (kgf) versus Binder Concentration (% w/v) of Chloroquine phosphate Tablets produced by Wet Granulation Method.

There is an increase in the crushing strength as the binding concentration increases with all binder types. PVP has the highest crushing strength at all binder concentrations investigated. The crushing strength of chloroquine tablets containing Enzyme-hydrolyzed starch was higher than that containing NCS at all binder concentrations.

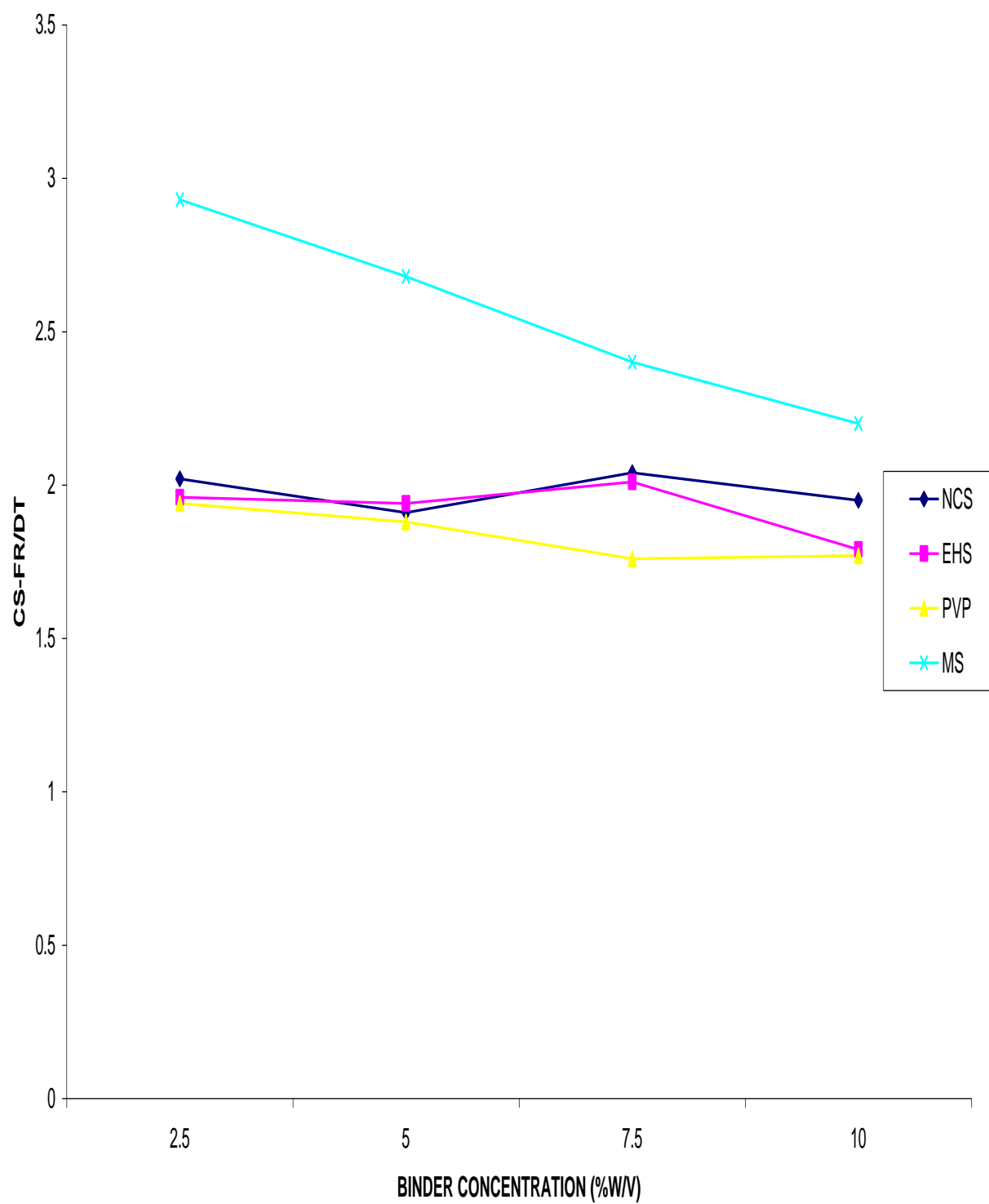


Figure 4.6: Graph of CSFR/DT versus Binder Concentration (% w/v) of Chloroquine phosphate Tablets produced by Wet Granulation.

CSFR/DT index rose slightly at 7.5 % w/v binder concentration for NCS and EHS before it decreased. For PVP and EHS there was decrease in the values as the binder concentration increases.

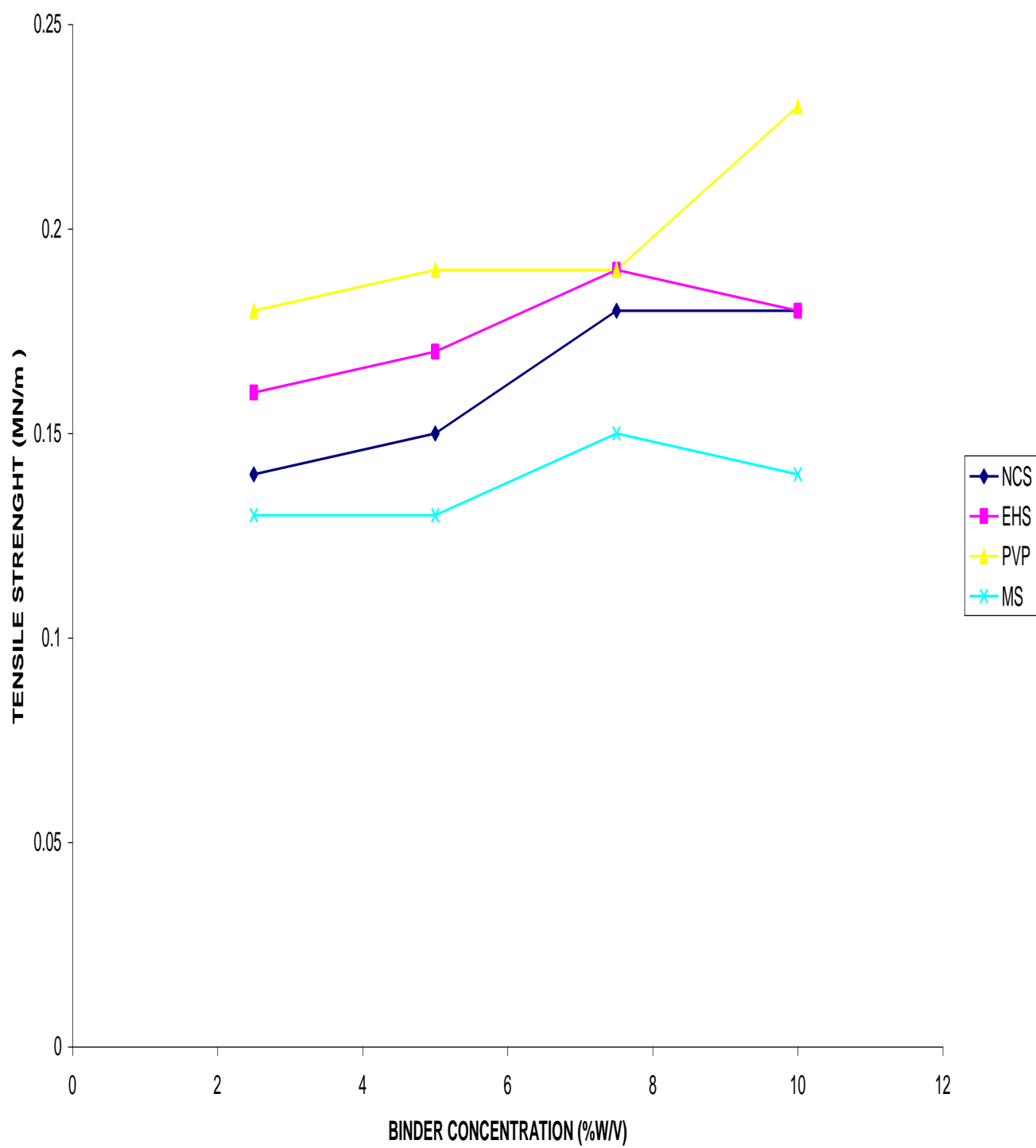


Figure 4.7: Graph of Tensile strength (MN/m^2) versus Binder concentration (% w/v) of Chloroquine phosphate Tablets produced by Wet Granulation.

The graph showed that there was increase in the tensile strength as the concentration of binder concentration increases for all the starches but for a common trend observed in EHS, NCS and MS. where there was slight reduction instead of an increase.

4.8 Dissolution profile

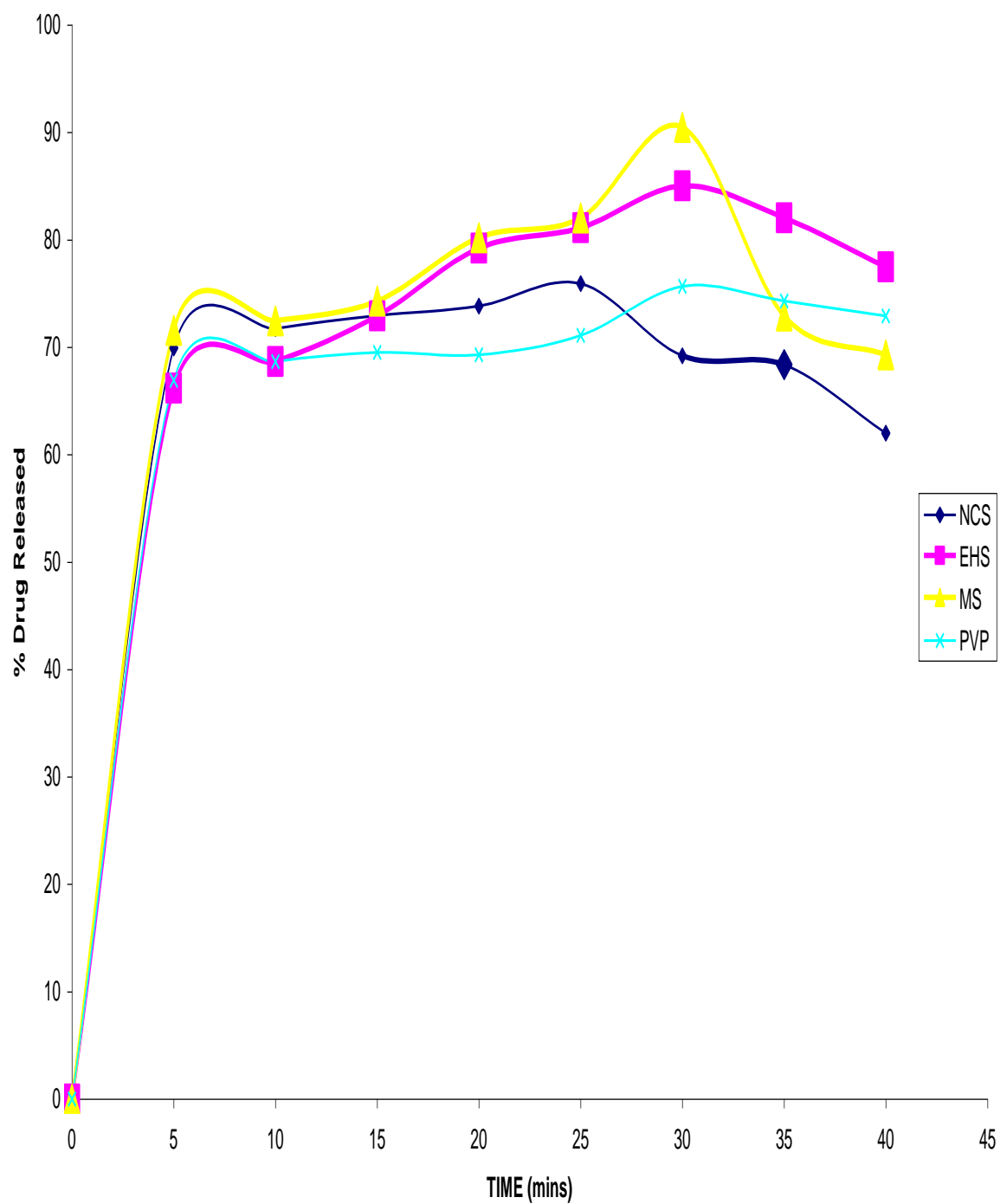


Figure 4.8: Graph of % Drug Released versus Time (min) of Chloroquine

Phosphate tablets containing 7.5 % w/v Binder Concentration.

There was increase in the amount of drug released as the time increases. This result indicated that more than 70 % of the drugs were released after 30 min.

4.7 Evaluation of Tablet Properties of Tablets produced by Direct Compression.

The properties of Chloroquine phosphate Tablets produced by direct compression are shown in Table 4.7.

Table 4.7: Evaluation of Tablets produced by Direct Compression

Binary mixture of MCC:EHS	Mean weight (mg)	Thickness (mm)	Diameter (mm)	TS (MN/m ²)	CS (kgf)	FR (%)	DT (min)	CS-FR
0 : 100	630.1	3.32	11.0	0.09	5.0	1.20	70	3.8
25 : 75	625.2	3.28	10.9	0.08	5.5	1.14	75	4.36
50 : 50	625.0	3.28	11.0	0.11	6.0	0.60	90	5.4
75 : 25	630.3	3.24	10.0	0.13	6.5	0.55	100	5.95
100 : 0	632.5	3.25	10.0	0.14	6.9	0.50	120	6.4

Key:

EHS = Enzyme Hydrolyzed starch FR = Friability

CS = Crushing Strength DT = Disintegration Time

MCC = Microcrystalline cellulose (Avicel^R)

The values for the uniformity of weights for the tablets range from 625.2 – 632.5 mg, this falls within the official limits specified by the BP. (2002). The values of the diameter

were determined using micrometer screw gauge and the values for thickness ranges between 3.24 – 3.32 mm.

The result showed increase in the Tensile Strength as the concentration of MCC increases, this is an indication that MCC as a binder produces harder and more compact tablets compared to EHS. There was increase in the crushing strength as the proportion of MCC increases.

CHAPTER FIVE

DISCUSSION

5.1 Preliminary Investigation of Starch

The percentage yield of Native cassava starch obtained from *Manihot esculenta* tubers was 12 %w/w and the percentage yield of the Enzyme Hydrolyzed starch (EHS) obtained from NCS after 6 h of enzymatic hydrolysis was 85 %w/w. There was a high yield of the EHS as a result of large proportion of the starting material (NCS) which was converted to EHS with minimum losses. This may be related to the fact that enzymatic hydrolysis is specific in nature and it produces fewer by-products when compared to acid hydrolysis (Aiyer, 2002). The processes and conditions of enzymatic hydrolysis are milder and much simpler than acid hydrolysis.

The results obtained for the organoleptic properties of EHS, NCS and MS are also shown in Table 4.1 and it shows that the properties of odour, colour, taste and texture for NCS were retained in EHS. This implies that the physical characteristics of the NCS were not tampered with during the enzymatic hydrolysis.

This observation was confirmed by the blue-black colouration obtained for both materials which indicates presence of starch in the two materials (Ocheja, 2000).

The results obtained for the micromeritics and physical investigations for the starches are presented in Table 4.2 and Table 4.3 and the moisture content for both NCS and EHS did not exceed the limit of 15% as specified in the B.P. (2002). Moisture content is a very important physicochemical property, it plays a vital role in tablet formulation as it affects other properties of a material such as flow property

and stability of a product. Pharmaceutical excipients are greatly affected by moisture because a host of these excipients have the capability of absorbing moisture i.e. they are hygroscopic in nature and therefore serve as a nutrient media for the growth of microorganism compromising the quality of the product (Aulton, 2007). It is also known to modify the flow and mechanical properties of many powders including starches (Adane *et al*, 2006) and it affects parameters such as weight and content uniformity (Musa *et al*, 2008).

It is very important to have the knowledge of moisture content where controlled powder flow or compaction is critical (Apeji, 2010).

The pH of NCS was slightly acidic (6.25) compared to EHS (6.96) which is more to the neutral range. The pH obtained for M.S. B.P was 6.5 which is slightly acidic. The B.P. 2002 indicated that M.S. B.P is a weak acid. Microscopical examination of NCS and EHS showed that they are spherical in shape (See Plate 4.1 and 4.2 respectively)

The physical properties of NCS, EHS and MS are presented In Table 4.3. The values obtained for the angle of repose are 33.3° , 26.6° and 26.0° respectively. Angle of repose is an indication of flowability of a substance whether powder or granule. This is dependent on the cohesive nature of the powder and the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive (Staniforth and Aulton, 2007).

Powders with angle of repose greater than 50° have unsatisfactory flow properties, whereas minimum value gives close to 25° corresponding to very good flow properties (Staniforth and Aulton, 2007). Of primary importance, when handling a drug powder, are its flow characteristics when limited amounts of drug

are available and these can be evaluated by measurements of bulk density and angle of repose. These are very useful parameters for assessing the impact of changes in drug powder properties as new batches become available (Aulton, 2007).

NCS has angle of repose of 33.3° which can be said to have passable type of flow, while EHS has 26.6° and it can be said to have good type of flow (Aulton, 2007). The values obtained for all the starch powders fell within the range showing that they have good flow properties while that of EHS can be comparable to M.S B.P. (Musa *et al*, 2008).

There is a correlation between the flow rate and angle of repose. The lower the angle of repose, the faster the flow rate and vice versa (Aulton, 2007) and this was seen in the results shown in Table 4.3 where NCS has high angle of repose with high flow rate of 1.92 g/s, EHS with 26.6° has faster flow rate of 1.62 g/s and M.S with 26.0° has a faster flow rate of 1.50 g/s. The flow rate of the starches is ranked in the order MS > EHS > NCS. There can be minimization of weight variation problems in tablets formulation if the starting material exhibits good flow property. The value of the bulk and tapped densities obtained are also shown in Table 4.2. The values obtained for NCS are higher than those obtained for EHS and MS. The tapped density is usually higher than the bulk density (Apeji, 2010), and this is because of diminished void spaces as a result of a change in bulk volume and this was produced by a rearrangement of packing geometry of the particles resulting in a tightly packed powder bed. Also the bulk density is always less than the true density of its component particles because bulk powder contains interparticulate pores or voids (Stanford and Aulton, 2007)

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates and a consolidated powder is likely to have a greater arch strength than a less consolidated powder and may therefore be more resistant to flow. Hence rapid consolidation is essential for uniform filling of tablet machines (Aulton, 2007). The results from this study show that EHS and MS consolidate less easily than NCS.

Powder porosity result is also shown in Table 4.2 and it shows that there is decrease of powder porosity as there is an increase in bulk and tapped densities. Carr's index (C.I) is a simple parameter that can be determined with small quantities of powder and it was developed to evaluate the flowability of powder. NCS has C.I of 16.67 % which can be said to be a good type of flow while EHS has 9.62 % and MS has 10.9 % which can be said to have excellent types of flow (Aulton, 2007).

A Hausner's ratio (HR) of less than 1.25 indicates good flow while greater than 1.5 indicates poor flow (Aulton, 2007). EHS has Hausner's ratio of 1.08, MS has 1.17. This is an indication that it has better flow property than NCS with HR of 1.2. All the starches fall within range, hence they all have good flow in the ranking order $EHS < MS < NCS$. The results obtained indicate that both MS and NCS densified more than EHS (Magnus and Anthony, 2002).

Carr's index and Hausner's ratio are one point determinations and do not always reflect the ease or speed with which consolidation of the powder occurs. Indeed, some materials have high indices, suggesting poor flow, but they consolidate rapidly and vice versa (Wells and Aulton, 2007).

The indices of compressibility (C.I and H.R) gives a measure of the ability of a material to be reduced in volume under pressure and the indication of the likely flow behaviour of granules when subjected to compression forces to form compact mass (Gideon *et al*, 2012).

The swelling power and moisture sorption capacity of each material too, are shown in Table 4.3. NCS has highest swelling powder of 1.45 than EHS with 1.25 and MS with 1.27. Tester *et al*, (2004) suggested that the swelling power of starch was attributed to its amylopectin content. The higher the amylopectin content the greater the swelling capacity.

The moisture sorption of EHS is 8 while that of NCS is 11 and MS is 10.5. The marked differences shown in Table 4.3 indicate that EHS is less hygroscopic in nature and so will not likely predispose formulations containing EHS to stability problems hence may form a more stable tablet. According to Ohwoavworhua and Adelakun (2005) moisture sorption capacity is a measure of moisture sensitivity of a material and it reflects the relative physical stability of the tablet formulated with the material when stored under humid condition.

EHS has low moisture sorption than MS and NCS, this is an indication that MS and NCS have better swelling than EHS and would result in quick rupture of tablets (Iwuagwu 1986).

Both starches have higher solubility in hot water than cold water. Starches are practically insoluble in cold water. However as the temperature increases, water penetrate more into the amorphous region of the starch granules resulting in more hydration and dissolution (Huijbrecht, 2008).

From the study it was observed that Enzymatic hydrolysis of starch did not modify its hygroscopic nature.

5.2 Physicochemical Properties of Granules

The physicochemical properties of EHS granules for all the batches are presented in Table 4.5, these comprise the bulk and tapped densities, Carr's index, Hausner ratio, flow rate, angle of repose, sieve analysis and percentage moisture loss.

All materials exhibit a better flow in the granular state than when it was in the powdered form and this is because many powders, because of their small sizes, irregular shapes or surface characteristics are cohesive and do not flow well, granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties (Summers and Aulton, 2007).

The values of all the angle of repose are in the range of good flow (Wells and Aulton, 2007).

For all the batches, the tapped density is higher than the bulk density. The percentage compressibility (Carr's index) and Hausner ratio express the difference between the bulk and tapped densities and the ratio of tapped to bulk density. These indices give a measure of the ability of a material to be reduced in volume under pressure and the indication of the likely flow behaviour of granules when subjected to compressional forces to form compact mass. It has been reported that the flow of the granules is better when Carr's index is lower (Okpanachi.2012).

The Hausner's ratio generally reduced with increase in binder concentration. The lower the index, the better is the predicted flow of the granules (Oyi, *et al.*,

2009). At binder concentration of 7 and 10 % w/v, the Hausner's ratio of NCS and EHS granules reduces with increase in binder concentration. Although all the Hausner's ratio for all the starches falls within the limit, they have a ratio less than 1.25 and it is an indication of a good flow (Stanforth and Aulton, 2007).

The result of Carr's index for all the batches shows that they have excellent type of flow (Aulton, 2007). The EHS granules have a better flow rate than the powder and this shows that changes in particle size and shape generally lead to better flow properties (Aulton, 2007).

5.3 Evaluation of Chloroquine phosphate Tablets Produced by Wet Granulation Method.

The results for the uniformity of weight, tablet thickness, diameter, crushing strength, friability and disintegration time are presented in Table 4.6.

The values of the weight of chloroquine tablets produced range from 300 – 315±1.50 mg. The values are within the acceptable limits of B.P 2002 for the respective weight of the tablets. The B.P specification states that for tablet weights > 250 mg, ± 5 % weight variation is allowed. This means that all the batches passed the weight uniformity test.

The uniform filling of the die cavity was as a result of good flow properties of the granules and was also enhanced by the addition of Glidant. Rawlings, 2004 stated that an assumption that the variation in the weight of individual tablets is a valid indication of the corresponding variation in the drug content.

The diameter was determined by the diameter of the punch and die cavity and the values are presented in Table 4.6. The thickness of the tablets obtained is in the

range of 2.48 – 2.88 mm and this variation can be due to the compressibility of the materials and/or the compression force applied (Aulton, 2007).

The crushing strength (CS) increased with increase in the binder concentration for all the binder types this is in consonance with the work of Ogaji and Okafor (2009). The values are shown in Table 4.6 and are in the order of PVP > MCS > NCS > MS. The CS is the measure of the structural strength of the tablets as provided by the binding agents during the process of compression, it is the applied load which when applied diametrically to a tablet causes fracture. Also reports have shown that the strength of tablet depends on the magnitude of plastic deformation occurring during compression (Alebiowu and Itiola, 2006)

The CS is an index used to measure tablet hardness. Tablets are held together by binders that act through Van der Waal's forces of attraction, frictional and mechanical forces, and forces due to the formation of solid bonds (Musa *et al*, 2010). The present work shows that EHS offers better bonding than NCS.

Friability (FR) is the measure of the weakness of tablet, it gives an indication of the likely edge damage that would occur when the tablets are handled during packaging, transportation and dispensing. There was general decrease in friability as the binder concentration increases (Figure 4.3), this can be attributed to formation of stronger bonds which conferred resistance to tablet fracture and abrasion (Itiola *et al.*, 2006). For the binder concentrations, the friability of tablets was found to be in the order MS > NCS > EHS > PVP.

The BP. 2002 states that the time taken for a tablet to disintegrate when immersed in some test fluid should not exceed 15 min for uncoated tablets. Tablets disintegrate by swelling of the disintegrant which generate a swelling force,

capillary action and breakdown of intermolecular forces resulting in development of a repulsive force between particles (Ngwuluka *et al*, 2010). Disintegration time (DT) of tablet increased with increase in binder concentration, this is as a result of increase in bond formation of the tablet as the binder concentration increases. The values for DT for all the batches are presented in Table 4.6 and all the tablets disintegrate within 15 mins, this implies that they all pass the DT test. The disintegration time are in the order PVP > EHS > NCS > MS.

The CS-FR index of all the batches increased with increase in the binder concentration and it follows the order PVP > EHS > NCS > MS. This index is a better tool for measuring the quality of tablet, it measures the mechanical strength of tablets better than CS alone or FR alone. It takes into account both the strength and the tendency of the tablet to fracture (Ogagi and Okafor, 2009). The higher the index the stronger the tablets.

The CSFR/DT is used to measure the strength and weakness of tablet, it also evaluates all the negative effects of these parameters on the disintegration time (Ogagi and Okafor, 2009). The results are shown in Table 4.6. At 2.5 % w/v and 5 % w/v binder concentration, there was decrease in the value obtained for NCS, MCS, PVP and MS, the disintegration time was in the order MS > EHS > NCS > PVP. Similar results were obtained at 5 % w/v and 10 % w/v binder concentration as well. 7.5 % w/v binder concentrations was chosen for dissolution test because it was the minimum concentration at which all the tablets passed crushing strength, friability and disintegration tests.

The results of the dissolution profile are shown in the appendices A.3 (Page 125). The dissolution efficiency (D.E.) which is the percentage of drug released

after 30 min. was greater than 85 % for NCS, EHS and MS. The order of ranking of D.E was $PVP < EHS < NCS < MS$.

All the tablets passed dissolution test, based on B. P (2002) specification, which states a minimum of 70 % drug should be released after 30 min. It can be observed from the results obtained that the dissolution of Chloroquine phosphate tablets correspond with the disintegration – dissolution theory which proves that disintegration usually play a vital role in dissolution process since it determines to a large extent the area of contact between the solid and the liquid media (Odeku and Itiola, 2006).

5.4 Evaluation of Chloroquine Tablets Produced by Direct Compression.

One of the requirements of a directly compressible excipient is that it must possess high dilution capacity. The dilution potential of an excipient is its ability to retain its compressibility and form a coherent compact when mixed with a poorly compressible drug (Apeji, 2010). Chloroquine Phosphate is poorly compressible in nature and is used as model drug to determine the dilution potential of EHS and MCC.

The weights of tablets obtained by direct compression were between 625.2 mg and 632.5 mg and they all fall within the ± 5 % weight variation specified by B.P (2002) for all tablets of theoretical weight greater than 250 mg. This implies that all the batches passed the weight variation test.

The crushing strength of the tablets decreases as the percentage of EHS in the binary mixture increases, tablets produced with 0 % and 25 % EHS have lowest crushing strength, the tablets produced by MCC were well compressed and the crushing strength increases as the percentage of MCC increases. The strength of

tablet depends on the magnitude of plastic deformation occurring during compression. Therefore MCC undergoes higher plastic deformation than EHS (Nyström *et al*, 1993). This result goes in line with the findings of Zhang *et al*, 2003 on direct compressible binders which indicated that MCC showed excellent compact hardness, this was attributed to the significant plastic deformation that occurs in MCC during compression bringing an extremely large surface area into close contact, facilitating hydrogen bond formation between the plastic deformed and adjacent cellulose particles.

The friability increases as the proportion of MCC reduces and it increases as the proportion of EHS increases. This is because MCC form stronger bonds which confer resistance to fracture and abrasion compared to EHS (Itiola *et al*, 2006.). All the tablets passed friability test except the batches containing 75 % and 100 % EHS proportion in the binary mixture which has friability values higher than the acceptable standard of 1 % (BP. 2002).

The disintegration time obtained for all the batches are above 60 min. The tablets continued to swell without dissolving completely on time, this could be because of high swelling capacity of MCC and because it forms very strong interparticulate bonds even at low pressure (Bulami, 1991). This agrees with the findings of Apeji (2010) that all the tablets formulated with MCC in direct compression did not disintegrate before 60 min.

The CS – FR index reduced with increase in the proportion of EHS it increases as the proportion of MCC increases. This index is a measure of the mechanical strength of tablet (Ogaji and Okafor, 2009). The result shows that MCC form stronger tablets than EHS. The results for the dissolution profile of the tablets

are presented in appendix A. 3.1 pg.127. The tablets did not release their active ingredient even after 60 min. of the study. This is because MCC forms very strong interparticulate bonds with simultaneous reduction in porosity thereby reducing the uptake of water that aids disintegration (Bulami, 1991).

5.5 Mechanical properties of Chloroquine phosphate formulation at various binding Concentrations.

The results obtained for tablets produced by wet granulation and direct compression methods are shown in table 4.6 and 4.7 respectively. It was observed from compacts formed from wet granulation method that the tensile strength increases as the binder concentration increases, this is as a result of stronger bond formation and more interparticulate interaction (Uhumwanglus *et al*, 2006). The ranking is in the order PVP > EHS >NCS >MS. PVP has the highest tensile strength followed by EHS. This could be due to high binding ability of PVP.

For direct compression, as the proportion of MCC increases, the tensile strength also increases. This is due to high binding ability of MCC.

CHAPTER SIX

SUMMARY, CONCLUSION AND RECOMMENDATION

6.1 SUMMARY

The modification of native cassava starch sourced from fresh tubers of *Manihot esculata* by enzymatic hydrolysis produced a derivative known as enzyme-hydrolyzed starch (EHS). *Manihot esculata* tubers yielded 20 % w/w starch, while EHS gave a yield of 85 % w/w. Preliminary investigation was carried out on both starches and they both showed presence of starch with iodine test and their particle size ranges between 2- 12 μm .

EHS showed improvement in its physicochemical properties over that of NCS, there was better flow rate and compressibility properties than NCS. The granules were formed with various binder concentrations and they all possessed good flow, however there was increase flow rate as the binder concentration increases.

The dilution potential determined for both EHS and MCC confirms that MCC had enhanced and superior bonding effects than EHS.

Chloroquine phosphate tablets produced by wet granulation method passed all the required tests such as crushing strength, friability test, disintegration test and weight variation test. However the crushing strength was found to increase as the binder concentration increases in the order PVP > EHS > NCS > MS while friability decreases in reverse order.

Chloroquine phosphate tablets produced by direct compression passed all the required tests such as crushing strength, friability test and weight variation test, however the tablets failed the disintegration test.

6.2 CONCLUSION

It can be concluded that

- I. Modification of *Manihot esculata* by enzyme hydrolysis produces enzyme-hydrolyzed starches with enhanced physicochemical properties compared to Native cassava starch (NCS).
- II. The tablet evaluation shows that EHS has more binding properties compared to NCS when used in wet granulation.
- III. Modification of *Manihot esculata* by enzyme hydrolysis produced material that is suitable as direct compression excipient.
- IV. EHS is cheaper and has the capability of being substituted as binder for Maize Starch BP.

6.3 RECOMMENDATIONS

Further works that can be carried out sequel to this work are:

- i. Evaluation of enzyme- hydrolyzed starch as binder in sustained released tablet formulations.
- ii. The modified starch should be viewed under a scanning electron microscope in order to study the surface morphology of the derived starch.

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APPENDICES

A.1.1 Particle size distribution for NCS

Sieve size (µm)	Retained	% Retained	Cumulative Retained (%)
500	0.48	2.52	2.52
250	1.62	8.50	11.02
150	0.53	2.78	13.80
90	2.18	11.43	25.23
75	2.33	12.22	37.45
Pan	11.93	62.56	100.00

A 1.2 Particle size distribution for EHS

Sieve Size	Retained	% Retained	Cum.Retained (%)
500	11.36	57.72	57.72
250	4.26	21.65	79.37
150	0.16	0.18	79.55
90	1.57	7.98	87.53
75	0.87	4.42	91.95
Pan	1.46	7.42	100

A 1.3 % Cumulative oversize of particle size analysis of NCS, MS and EHS

SIEVE	%CUMM.	%CUMM.	%CUMM.
SIZE(μm)	FREQ.(NCS)	FREQ.(MS)	FREQ.(EHS)
500	2.52	64.21	57.72
250	11.02	78.02	79.37
150	13.80	80.23	80.18
90	25.23	86.26	88.16
75	37.45	95.04	93.58
0	100.00	100.00	100.00

A 2.1 Particle size distribution for the granules.

A1

Sieve size	Retained	%retained	Cumm. Freq. %
500	7.57	78.20	78.20
250	1.16	11.98	90.18
150	0.26	2.69	92.87
90	0.61	6.30	99.17
75	0.08	0.83	100

A2

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.12	82.19	82.19
250	1.20	12.15	94.34
150	0.24	2.43	96.77
90	0.26	2.63	99.40
75	0.04	0.40	100

A3

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.00	82.99	82.99
250	1.10	11.41	94.4
150	0.25	2.59	96.99
90	0.25	2.59	99.58
75	0.04	0.41	100

A4

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.10	82.23	82.23
250	1.19	12.08	94.31
150	0.26	2.64	96.93
90	0.27	2.74	99.69
75	0.03	0.3	100

B1

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.4	84.93	84.93
250	1.2	12.13	97.06
150	0.15	1.52	98.58
90	0.10	1.01	99.59
75	0.04	0.40	100

B2

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.35	84.00	84.00
250	1.23	12.37	96.37
150	0.12	1.21	97.56
90	0.20	2.01	99.59
75	0.04	0.40	100

B3

Sieve size	Retained	%retained	Cumm. Freq. %
500	9.14	93.08	93.08
250	0.61	6.21	99.29
150	0.02	0.20	96.49
90	0.04	0.41	99.9
75	0.01	0.10	100

B4

Sieve size	Retained	%retained	Cumm. Freq. %
500	9.00	90.18	90.18
250	0.9	9.02	99.2
150	0.02	0.20	99.4
90	0.04	0.40	99.8
75	0.02	0.20	100

C1

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.50	85.4	85.4
250	1.2	12.06	97.46
150	0.1	1.01	98.47
90	0.1	1.01	99.48
75	0.05	0.50	100

C2

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.03	80.62	80.62
250	1.29	12.95	93.57
150	0.26	2.61	96.18
90	0.33	3.31	99.57
75	0.05	0.50	100

C3

Sieve size	Retained	%retained	Cumm. Freq. %
500	7.74	77.4	77.4
250	1.43	14.3	91.7
150	0.06	0.6	92.3
90	0.69	6.9	99.2
75	0.04	0.4	100

C4

Sieve size	Retained	%retained	Cumm. Freq. %
500	7.89	78.9	78.9
250	1.3	13	91.9
150	0.16	1.6	93.5
90	0.11	1.1	94.6
75	0.04	0.4	100

D1

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.54	89.61	89.61
250	0.83	8.71	98.32
150	0.07	0.73	99.05
90	0.06	0.63	99.68
75	0.06	0.63	100

D2

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.6	86	86.00
250	0.9	9	95.00
150	0.4	4	99.00
90	0.02	0.02	99.2
75	0.08	0.8	100

D3

Sieve size	Retained	%retained	Cumm. Freq. %
500	9.01	91.01	91.01
250	0.8	8.0	99.09
150	0.07	0.71	99.80
90	0.01	0.10	99.90
75	0.01	0.10	100

D4

Sieve size	Retained	%retained	Cumm. Freq. %
500	8.50	85.86	85.86
250	1.3	13.13	98.99
150	0.08	0.81	99.8
90	0.10	1.01	100
75	0.10	0.10	100

A2.1 Properties of tablets produced by direct compression

Binary mix of MCC:EHS	Mean weight (mm)	Thickness (mm)	Diameter (mm)	CS (kgf)	FR (%)	DT (min)	CS- FR
0 : 100	630.1	3.32	11.0	5.0	1.2	70	3.80
25 : 75	625.2	3.28	10.9	5.5	1.14	75	4.36
50 : 50	625.3	3.28	11.0	6.0	0.60	90	5.4
75 : 25	630.3	3.24	10.0	6.5	0.55	100	5.95
100 : 0	632.5	3.25	10.0	6.9	0.50	120	6.4

A.3.1 DISSOLUTION TESTS

A.3.1: Dissolution test results for NCS.

Time (mins)	Abs (nm)	Amount dissolved (mg/1000ml)	% drug dissolved
5	0.767	174.82	69.93
10	0.787	179.37	71.75
15	0.800	182.34	72.94
20	0.810	184.61	73.84
25	0.833	189.85	75.94
30	0.759	173.00	69.20
35	0.750	170.95	68.38
40	0.68	155.02	62.00

A.3.2: Dissolution test results for EHS.

Time (mins)	Abs (nm)	Amount dissolved (mg/1000ml)	% drug dissolved
5	0.726	165.49	66.20
10	0.753	171.64	68.65
15	0.800	182.33	72.93
20	0.869	198.04	79.22
25	0.890	202.82	81.13
30	0.933	212.61	85.04
35	0.90	203.09	82.04
40	0.85	193.71	77.49

A.3.3: Dissolution test results for MS.

Time (mins)	Abs (nm)	Amount dissolved (mg/1000ml)	% drug dissolved
5	0.785	178.92	71.57
10	0.795	181.20	72.48
15	0.815	185.75	74.30
20	0.880	200.55	80.22
25	0.90	205.09	82.04
30	0.850	193.72	90.49
35	0.80	182.34	72.93
40	0.76	173.23	69.29

A.3.4: Dissolution test results for PVP.

Time (mins)	Abs (nm)	Amount dissolved (mg/1000ml)	% drug dissolved
5	0.734	167.31	66.92
10	0.753	171.64	68.65
15	0.762	173.80	69.52
20	0.760	173.23	69.29
25	0.780	177.78	71.11
30	0.830	189.16	75.67
35	0.815	185.75	74.30
40	0.800	182.34	72.93

A.3.5: Dissolution test results for direct compression

Time (mins)	Abs (nm)	Amount dissolved (mg/1000ml)	% drug dissolved
5	0.270	61.69	24.68S
10	0.300	68.52	27.31
15	0.320	73.07	29.23
20	0.372	84.91	33.96
25	0.384	87.64	35.06
30	0.406	92.65	37.06
35	0.400	91.28	36.51
40	0.380	86.73	34.69

Conc (µg/ml)	Abs(nm)
0.015265	0.01
0.03125	0.014
0.0625	0.017
0.125	0.044
0.25	0.125
1	0.436

A6.1 Calibration curve parameters for chloroquine phosphate tablet

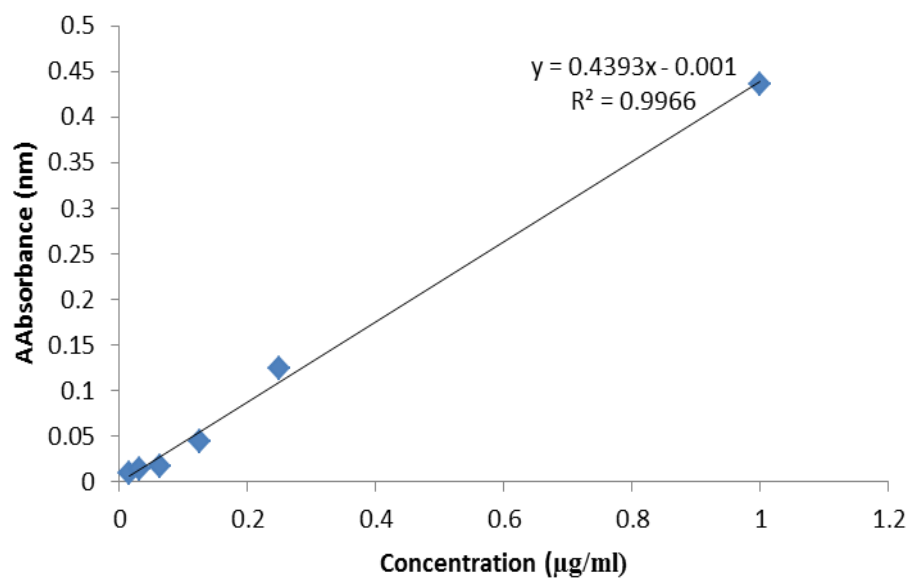


Figure A1.1 Calibration curve for chloroquine phosphate.