ADISS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

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DEPARTEMENT OF PHARMACEUTICS AND SOCIAL PHARMACY

PREPARATION, CHARACTERIZATION AND EVALUATION OF CROSS-LINKED SWEET POTATO [*IPOMOAE BATATAS (L.) LAM*.] STARCH FOR SUSTAINED RELEASE TABLET FORMULATION

BY

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AUGUST, 2023

ADDIS ABABA, ETHIOPIA

Preparation, Characterization and Evaluation of Cross-Linked Sweet Potato [*Ipomoea batatas (L.) Lam.*] Starch for Sustained Release Tablet Formulation

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A Thesis submitted to the Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, in partial Fulfilment of the Requirements for the Degree of Master of Science in Pharmaceutics

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August, 2023
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This is to certify that the thesis prepared by Asnake Woldeyohannes, entitled: "Preparation, Characterization, and Evaluation of Cross-linked Sweet potato [*Ipomoea batatas (L) Lam*.] Starch for Sustained Release Tablet Formulation" and submitted in partial fulfilment of the requirements for the Degree of Master of Science in Pharmaceutics complies with the regulations of the University and meets the accepted standards concerning originality and quality.

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ACKNOWLEDGEMENTS

All glory to the All-Powerful God, who has enabled everything in my life. He has sustained me throughout the course of writing my thesis.

I would like to express my gratitude for my academic advisers, Dr. Gebremariam Birhanu for his supervision from the beginning to the finish of this study and Kebede Wondu for his suggestions, follow-up, and helpful direction.

I extend my heartfelt thanks Addis Ababa University and Ambo University for sponsoring my postgraduate studies. I would like to thank the School of Chemical and Bio-Engineering at Addis Ababa Institute of Technology and Addis Ababa University for letting me use their rotating Viscometer.

I would like to say thanks to Cadila Pharmaceutical PLC for providing free access to the FT-IR Spectrophotometer and East Africa Pharmaceutical PLC for graciously giving me access to their compression equipment and contributing the raw material for glibenclamide and microcrystalline cellulose.

Finally, yet importantly, my parents' ambitions, who have sacrificed a great deal for my higher education, are also being realized with the completion of my studies in addition to my own.

I would like to express my gratitude to my mother, brother, and the Cheryl Whinna family for all their constant support. I sincerely value their love, sacrifices, encouragement, inspiration, and unconditional mental support. I am also grateful to my colleagues and friends for encouraging me to accomplish this thesis.

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ABBREVIATIONS AND ACRONYMS

BCS: Biopharmaceutical classification system

BP: British pharmacopeia

CLSPS: Cross Linked sweet potato starch

CMS: Carboxymethyl starch

DCL: Degree of Cross-linking

ECH: Epichlorohydrin

FDA: Food and Drug Administration.

GLB: Glibenclamide

GRAS: Generally Recognized as Safe

HCl: Hydrochloride

$NaHCO_3$: Sodium bicarbonate

NS_S: Native starches

$POCl_3$: Phosphoryl chloride

PV: Peak viscosity

PVP: Polyvinyl Povidone

SHMP: Sodium hexametaphosphate

SI: Swelling Index

SPS: Sweet potato starch

SR: Sustained release.

SRDDS: Sustained Release Drug Delivery System

STMP: Sodium Tri metaphosphate

STPP: Sodium tripolyphosphate

USP: United States pharmacopeia

ABSTRACT

Along with cellulose and chitin, starch is one of the most prevalent biopolymers on earth and serves as a significant reserve polysaccharide in higher plants. Starch is an important ingredient in many products used in the food, pharmaceutical, and other industries. Despite its importance, starch is rarely regarded as an ideal raw material because of its uncomplimentary properties. Thus, modifications such as physical, chemical and enzymatically modifications are necessary to produce starch derivatives with improved pharmaceutical properties. The aim of this study was to chemically cross-link sweet potato (*Ipomoea batatas (L.) Lam*) starch using sodium hexametaphosphate and evaluate its potential for sustained release applications.

Sweet potatoes (Ipomoea batatas (L. Lam)) starch was extracted, and then it was subjected to three different concentrations (10%, 15% and 20%) of SHMP treatment to create cross-linked sweet potato starches (CLSPSs): 10%-CLSPS, 15%-CLSPS, and 20%-CLSPS, at a temperature of 55°C, and the cross-linking process took place for 8 hours. The degree of cross-linking for 10%-CLSPS, 15%-CLSPS, and 20%-CLSPS were 67.73% $\pm$1.86, 75.35% $\pm$ 2.99, and 77.45% ± 0.34, respectively. Increasing the concentration of sodium hexametaphosphate used for cross-linking starch leads to higher degree of cross-linking, which in turn reduces the solubility and swelling power of the starch. This is because the cross-linking process produces a more rigid and compact structure, making it more difficult for water molecules to penetrate and interact with the starch molecules. Moreover, in the moisture sorption study, it was observed that the water uptake capacity of the starch decreased with an increase in cross-linking. Furthermore, the cross-linked starch exhibited improved physical properties such as enhanced compressibility, powder density, flowability, and heat stability as compared to its native starch. X-ray crystallography showed that the CLSPSs had a crystal structure with a diffraction angle of 15.33°, 17.22°, and 22.96°, and nearly the same crystallinity as the native starch. SEM photographs showed minor morphological differences as it is observed on the powder surfaces of both native and CLSPS. The Fourier Transform Infrared Spectroscopy and Differential scanning calorimetry investigations supported the conclusion that there was no incompatibility between the model drug glibenclamide and CLSPS polymer.

Tablets were prepared using various amount of cross-linked starch by direct compression method the prepared tablets were evaluated for the physical properties such as weight variation, thickness, hardness, friability, disintegration time and in vitro drug release studies.

Preliminary studies result suggested the drug release characteristics from matrix tablets could be influenced by the concentration of cross-linking agent, and the ratio of cross-linked starch. Additionally, the suitability of methods used for determining these characteristics was also assessed. According to the study's results, the prepared tablets had satisfactory physical properties and met the standards. The tablets prepared with 10%-CLSPS showed a glibenclamide release percentage of 88% at 6 hours, while the tablets made with 15%-CLSPS released 85% of the drug at the same time. The tablets prepared with 20%-CLSPS released 81.2% of the drug close to 12 hours. The tablet matrix gelling capabilities of CLSPS, which created a gel-like network around the drug particles and slowed the rate of drug release, were thought to be responsible for the sustained-release properties of the tablets. The Higuchi's model and the Kors meyer Peppa's models were determined to best fit in-vitro dissolution data after being subjected to numerous drug release kinetics models. It was identified that the "n" value for the diffusional release exponent, which indicates that drug release processes involved both polymer erosion and diffusion, ranged between 0.6303 and 0.7367. The drug release pathways were consequently categorized as anomalous or non-Fickian diffusion. In conclusion, the study findings suggest that cross-linked sweet potato starch is a more favorable option for utilization in pharmaceutical formulations due to its superior sustained-release properties. Therefore, it can be considered as a viable substitute polymer for achieving sustained-release effects.

Keywords: *Cross-linked Starch, Glibenclamide, Matrix tablet, Sodium hexametaphosphate, Starch, Sweet potato (ipomoea batatas (L). Lam), Sustained release.*

1. INTRODUCTION

1.1 Starch

Starch is one of the most abundant biopolymers on earth, along with cellulose and chitin (Singh,*et al*., 2011). It is one of the most extensively distributed chemical molecules in nature being the form of plant materials that store energy (Rodríguez *et al.*, 1989). It is an important reserve polysaccharide in higher plants and has made up of repeated units of D-glucopyranose in which D-glucose units are connected by α-1,4 linkages. This natural polymer is mostly composed of two macromolecule: amylose (15-30%) and amylopectin (70-85%) a polymer with branching chains composed of significantly shorter chains of [α-1, 4] D- glucose residues linked by [α-1,6] D-glycosidic bonds (Costa Neto *et al.*, 2018), and a trace of other components such as proteins, a few of inorganic chemicals, and water. In addition, starch with a higher content of amylose is often utilized in pharmaceutical formulations as an excipient, serving to maintain the activity of active ingredients and act as an encapsulating agent. This allows for targeted delivery of medication to specific organs within the body (Nawaz, H *et al.*, 2020).

Starch can be extracted from plants with minimal processing, it's physicochemical and functional properties make it an attractive choice as a pharmaceutical excipient for various drug delivery systems and formulations. As pharmaceutical excipients, both native and modified starches have received a considerable attention, primarily in the food, polymers, and pharmaceutical sectors (Builders and Arhewoh, 2016). It is commonly regarded as a safe chemical and is so placed on the Generally Recognized as safe (GRAS) list of the US Food and Drug Administration (FDA). This is not only that starch is a widely available, inexpensive, and harmless ingredient, but also to how easily its physicochemical properties may be altered by chemical or enzymatic modification and/or physical treatment (Wondimu *et al.*, 2014). In the pharmaceutical industry starch from corn, rice, potato, and wheat are the most often used as a binder, diluent, filler/glidant, thickening agent, disintegrant, and release retarding agent after some chemical treatments. During tablet production, freshly made starch paste with a concentration of (5–20) % is commonly employed as a binder. It can also be used as a disintegrant in a variety of tablet formulations at (5–15) % concentration (Manek *et al.*, 2012).

Microscopically, starch granules can be observed as distinct structures that are composed of alternating sections of amorphous and crystalline lamellae. These lamellae are visible as concentric rings within the granule, which are primarily made up of the crystalline portion of the starch (Rodríguez *et al.*, 1989).

The crystalline portion of starch is frequently constituted of amylose and has a consistent pattern of densely packed glucose molecules. The amorphous component of starch, which frequently contains amylopectin, is made up of loosely packed glucose molecules arranged in a less regular manner. Starch's characteristics, such as viscosity and the temperature at which it gelatinizes, can be influenced by the proportions of amylose and amylopectin in it (Hoover, R., 2001).

1.2 Amylose and Amylopectin of starch

Starch's physical and functional characteristics are determined by the relative concentrations of amylose and amylopectin (Bertoft, E., 2017). The relationship between these two constituents can affect the structure of starch in terms of crystallinity, granule size, chemical composition, and polymer arrangement inside the granule (Wani *et al.*, 2012). Figure-1 shows the chemical structure of amylose and amylopectin in starch. Amylose is the most important component controlling the physicochemical properties of starches. When starch is heated in aqueous solutions, it expands irreversibly and its crystalline structure collapses, the molecular chains open, allowing them to collide with other starch chains to form a network, thickening the liquid a process known as gelatinization. Amylopectin can cause starch swelling, whereas amylose can prevent it (Wani *et al.*, 2012). Later affects the packing of amylopectin into crystallites as well as the arrangement of the crystalline lamella within starch granules. The amorphous regions of the semi-crystalline layers and the amorphous layers are composed of amylose and non-ordered amylopectin branches (Singh, Kaur, and McCarthy, 2007). This is critical for features like swelling and gelatinization that are related to water intake (Cornejo-Ramírez *et al.*, 2018).

In starch with greater quantities of branching amylopectin molecules, give viscosity to the cooked paste. Because their side chains and bulky structure prevent them from orienting closely enough to link together, they are rarely involved in gel formation (Kumar and Khatkar, 2017). However, under specific circumstances, they can still contribute to gel formation. For instance, when heated in the presence of specific substances, such as acid or sugar, some starches can create a gel. In these circumstances, the amorphous areas of the starch granule become more organized and form a gel (Tester *et al*., 2004). Although the amylose content of the starches differed only slightly, there was a substantial difference in functional properties such as swelling power, pasting characteristics, thermal transition temperatures in the differential scanning calorimeter, and resistance to in vitro amylase (enzymic) attack (Wang, Sharp and Copeland, 2011).

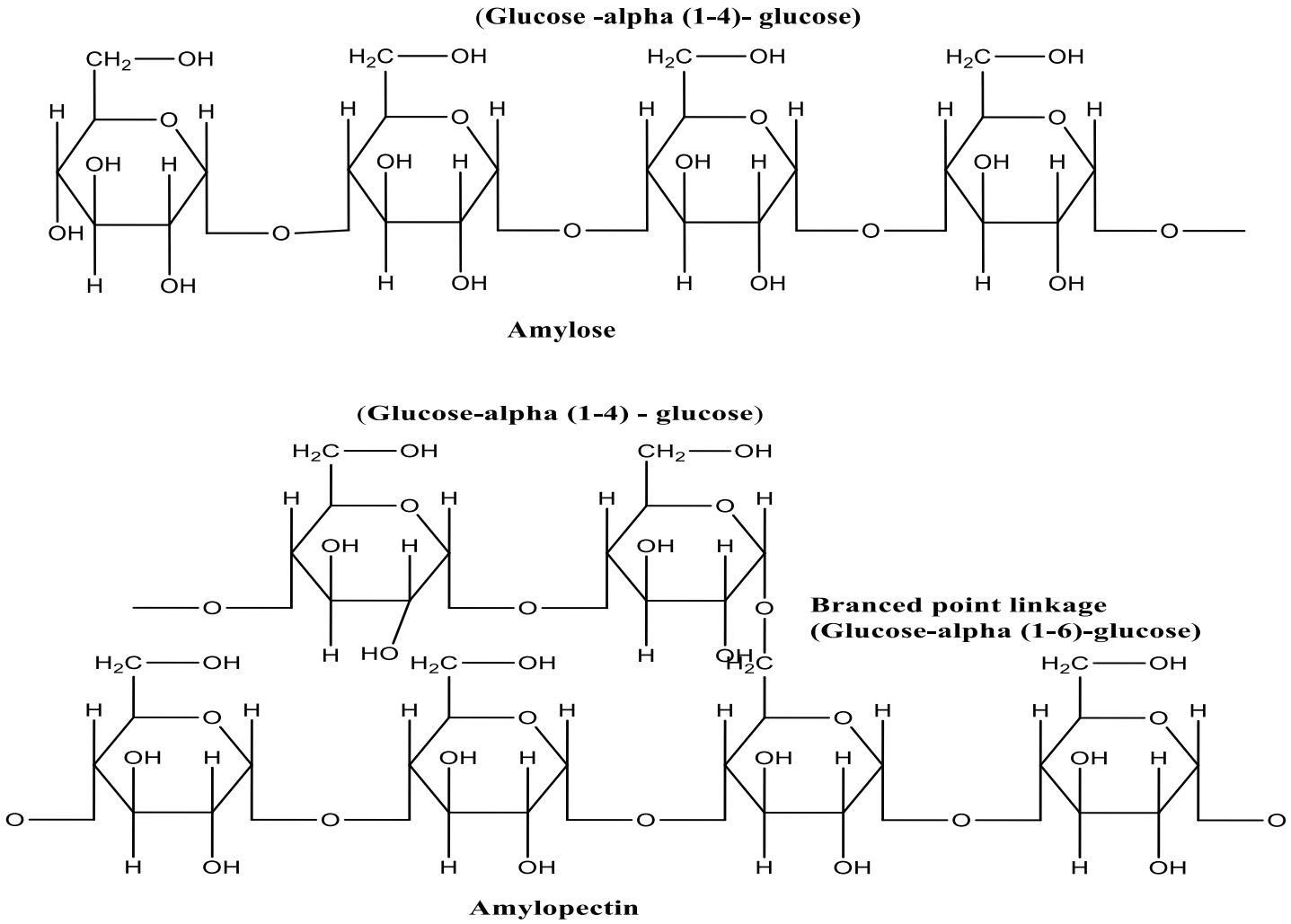


Figure 1: Chemical structure of amylose and amylopectin.

1.3 Sources of starch

The sources of starch vary based on the geographical area, notably the climate and tradition of a certain locality. Across the globe, the majority of research reports, commercial starches are mostly sourced from corn, potato, wheat, cassava, and sweet potato (Makroo *et al.*, 2021 and Troncoso and Torres, 2020). The physicochemical and functional properties of starch are influenced by its botanical sources, including factors such as amylose/amylopectin ratio, molecular weight, molecular structure, length of glucans, degree of amylopectin branching, non-carbohydrate impurities, and other thermal and rheological characteristics (Nwokocha *et al.*, 2009).

In Ethiopia, starch can be obtained from various plant sources, including *Plectranthus edulis* is known dinch, Enset (*Ensete ventricosum*, Musaceae), *Dioscorea abyssinica* (boyna), Anchote (*Coccinia*

abyssinica), godare (*Colocasia esculanta*), Yam (*Dioscorea abyssinica*). Yam can be explored for commercial starch production because of their high starch content of about 70 to 80% dry weight (Raji, A.O., 2020). Similarly, Cassava starch *(Manihot esculenta*) is a tropical valuable root crop, used both as food and industrial raw material, due to the high starch content in tubers. The source of starches can have an impact on the properties of pharmaceutical dosage forms, particularly in terms of solubility, viscosity, and swelling capacity. These characteristics can affect the performance of excipients in drug formulations. Therefore, it is important to consider the source of starches when selecting excipients for drug formulation and when substituting one type of starch with another (Rodríguez *et al.*, 1989).

1.4 Sweet potato (Ipomoea batatas (L.) Lam.) and its Starch

Sweet potato, scientifically known as *Ipomoea batatas (L.*) Lam., is a plant with tuberous roots that belongs to the Convolvulaceae family. It is known for its high sugar content, pleasant cooking odor, and various bioactive chemicals that offer nutritional and health benefits (Mitiku and Teka, 2017 and Wei, Lu and Cao, 2017). It is the world's most significant root crop, after rice, wheat, potatoes, maize, and cassava, but it ranks fourth in developing countries due to its importance as a food crop (Selamawit Abebe *et al.*, 2021). In Ethiopia, small-scale farmers grow sweet potatoes in the southern, southwestern, and eastern parts of the country for human consumption. It is the third most significant root crop produced, following Enset (*Ensete ventricosum (Wele) Cheesman*) and Potato (*Solanum tuberosum L.*) (Wassu Mohammed, 2015).

Sweet potatoes are rich in starch, accounting for almost 50–80% of the plant, and have been widely studied for culinary uses and industrial purposes (Nabubuya *et al.*, 2012). They are a low-cost and abundant natural resource, with tremendous promise as an industrial raw as a food additive, such as a thickener, stabilizer, or tissue reinforcing agent, to improve food retention, control water flow, and maintain food storage quality because of its high starch content (Rahman, Wheatley et Rakshit, 2003 and Mu *et al.*, 2017). The bioactive phytochemicals present in sweet potatoes are possible sources of antioxidants that can scavenge free radicals, minimize or block cellular damage, and lower metabolic oxidative stress, resulting in disease prevention and improved health (Amagloh *et al.*, 2021). This entire set of attributes makes it pertinent as a raw material for pharmaceuticals.

The composition of amylose and amylopectin in sweet potato can vary depending on the variety and growing conditions of the plant. However, studies have shown that sweet potato starch typically contains

around 20-25% amylose and 75-80% amylopectin (Kim *et al*., 2005). Its amylopectin is generally made up of three types of branching chains, A, B, and C, which are similar to the structure of other starches. As the main chain, the C chain is found at the reducing end of the amylopectin molecule (Chen, Z. 2003), the reducing end group is linked by -1,6 linkage, and the B chain is linked with one or more A chains. Sweet potato amylopectin is often dominated by its B chain (>11 glucose residues per long chain), and the A chain (11 glucose residues per short chain) is shorter than the B chain (Mu *et al.*, 2017).

As shown in figure 2, the Awassa83 variety of sweet potato was selected for this study based on it provide high yield of starch according to study done by (Wondu, K *et al.*,2018). It was developed by the Awassa Agricultural Research Center in Ethiopia. It is a relatively new variety that was released in 2004. The Awassa83 variety is a specific cultivar of sweet potato that is known for its high yield and disease resistance (Gobena *et al*., 2022).



Figure 2: Sweet potato (*ipomoea batatas (L). Lam*) Awassa83 variety.

1.5 Starch modification

Native starch's use in medicinal and industrial applications is limited due to its complicated polymeric structure and low water solubility, low compatibility and elastic compression characteristics, quick retrogradation, and lower capability to sustain heat breakdown (Shah *et al.*, 2016 and Nawaz, H *et al*., 2020). Fortunately, starch is suitable for modification due to the presence of a huge number of active hydroxyl groups on the surface so that this offers superior physical and chemical properties to native and is gaining popularity (Dai, Zhang, and Cheng, 2019). Modification of starch can reduce its

susceptibility to swelling, inadequate gelling properties, and inadequate paste clarity, These modifications are also intended to reduce retrogradation and the tendency of pastes to form gels, improve the texture of pastes or gels and the generation of films, and add hydrophobic groups, as a result of which, its necessary to broaden its potential usage in the food and pharmaceutical applications (Marta and Tensiska, 2017 and Costa Neto *et al.*, 2018). Starch modifications can broadly be classified in to Physical, chemical, and Enzymatic modifications (Dai, Zhang and Cheng, 2019).

1.5.1 Physical Modification

Physical modification of starches are changes in starch properties generated by physical treatment that do not result in chemical changes to the starch, other than limited glycosidic bond cleavages (BeMiller, 2018). Native starches are frequently modified to produce certain features such as solubility, texture, adhesion, and resistance to the heating temperature employed in industrial processes (Noman *et al.*, 2016). It causes variations in particle size, surface characteristics, solubility index, and functional characteristic of starch such as water absorption, swelling capacity, pasting, and gelation ability. These alterations have a direct impact on the modified starch's functional properties, selectivity, and applicability for diverse nutritional, medicinal, and industrial formulations (Nawaz, H *et al.*, 2020). Some of physical modifications including:

1.5.1.1 Pre-gelatinized starch (PGS)

In the presence of water and heat, the intermolecular bonds between starch molecules are broken down, allowing the hydrogen bonding site (the hydroxyl hydrogen and oxygen) to engage more water. This process is known as starch gelatinization. As a result, it can enhance the viscosity of the system and have an appropriate thickening property (Ma *et al.*, 2022). It is a popular form of modified starch that has a wide range of uses, particularly in the food and pharmaceutical industries. PGS sometimes known as "pre-gel" or "instant starch," is typically manufactured using a drum drier, a spray drier, or an extruder (Majzoobi *et al.*, 2011 and Ashogbon and Akintayo, 2014). Fully and partially pregelatinized starches are widely used as binders, diluents, and disintegrants in oral capsule and tablet formulations. These starches are commercially available and offer improved flowability and immediate compressibility after undergoing some level of pre-gelatinization (Gupta *et al.*,2012).

In Ethiopia, studies have explored the use of pre-gelatinized starches from Plectranthus edulis, Taro Boloso-I (Colocasia Esculenta Cultivar), and Enset as alternative direct compressible excipients, binders, and disintegrants in pharmaceutical formulations. For instance, (Balcha., 2016) reviewed the

use of pre-gelatinized starch from Plectranthus edulis and Taro Boloso-I (Colocasia Esculenta Cultivar) as direct compressible excipients, while wondimu *et al.*, 2014 investigated the use of pre-gelatinized Enset starch as a binder and disintegrant. When starch is fully pregelatinized, it becomes soluble in cold water, which makes it a suitable binder for wet granulation (Demissie, Y., 2018).

1.5.1.2 Retrogradation

The process of retrogradation is the joining of starch chains into organized crystalline structures, and the linear portion of starch is particularly susceptible to retrogradation (Zia-ud-Din, Xiong and Fei, 2017). However, retrogradation is sometimes promoted to modify the structural, mechanical, or organoleptic properties of certain starch-based products (Karim, Norziah and Seow, 2000). The hydrothermal process of starch retrogradation changes pregelatinized starch (amorphous) to a more resistant and compacted crystalline form known as resistant starch (RS), which may be found in several subtypes (Dai, Zhang and Cheng, 2019). Retrograded starch, also known as resistant starch type III, has been researched for its possible use as a pharmaceutical excipient due to its unique properties, including its capacity to form gels, its stability, and its biocompatibility. It can be employed as a binder, thickening, or disintegrant in a range of pharmaceutical formulations, such as tablets, capsules, and gels (Singh *et al*., 2007).

1.5.1.3 Microwave-Assisted Modification of Starch

Microwave radiation is electromagnetic radiation in the range of from 300MHz to 30GHz and is one of the physical methods used to improve the functional properties of starch. It is a very good source of energy and allows fast transfer of the energy into the interior of the material where the energy is converted into heat, along with a significant reduction of processing time when compared to conventional process (Lewicka, Siemion and Kurcok, 2015). Microwave radiation is now widely employed in a variety of processes such as heating, freezing, and sterilizing in both commercial and residential applications (Szepes, *et al.*, 2005). It is gaining importance as a processing technique in the production of modifies starch. It may be beneficial creating modified starches with certain properties for direct compression (DC) for example, microwave-assisted succinylation and acetylation modification of some locally obtained starches, from cassava and Plectranthrus edulis (P. edulis) respectively, and improve their properties (Rivero, Balsamo and Müller, 2009 and Lawal, M.V., 2019) and Microwave irradiation has several advantages as a processing technology, including speed, cost-effectiveness, heating selectivity, and environmental safety. However, microwave treatment has

drawbacks, including the possibility of developing thermally unstable or damaged materials due to uneven heat distribution (Lewicka, Siemion and Kurcok, 2015).

1.5.2 Chemical modification of starch

Chemical modification is the process of insertion of new chemical or functional into the starch molecule, resulting in significantly changed physicochemical characteristics (Ibikunle *et al.*, 2019). This changes the gelatinization, pasting, and retrogradation behavior of native granular starches. The chemical and functional properties obtained when modifying starch by chemical substitution are dependent on the starch source, reagent type required for the modification, the degree of substitution of the chemical reagent, reaction conditions (reactant concentration, reaction time, pH, and the presence of a catalyst) (Ashogbon and Akintayo, 2014). There are different types of chemical modifications that can be done to starch, such as esterification which can be achieved through acetylation. For example, starches from sweet potatoes (Ipomoea batatas L.) and water yam (Dioscorea alata L.) can all undergo this process (Bolade *et al*, 2015),

Sorghum starch has been studied as a potential alternative for modification in various applications, as highlighted by (Taylor, Singh and Sodhi, 2013). Another example is the utilization of Ofada rice starch as a sustained release polymer, as explored by (Okunlola, A. and Ogunkoya, T.O., 2015). Additionally, starch from corn, wheat, potato, and cassava has been subjected to etherification for the purpose of thickening and stabilization, while alternative methods such as cross-linking, hydrolysis, and oxidation have also been investigated for modification, as discussed by (Kavelani *et al.*, 2012 and S. Senanayake *et al.*, 2014). In general, starch's susceptibility to modification is determined primarily by the material's biodegradability and the presence of specific functional groups, when chemically modified starch exhibits different properties depending on the location of the hydroxyl group and the type of bond ((1,4)–glycosidic versus (1,6)–glycosidic). Reduction in the number of hydroxyl groups caused by chemical alternation that can improves the hydrophobicity and different characteristics of the starch (Emeje, M. and Blumenberg, M., 2020 and Lewicka, Siemion and Kurcok, 2015). It has been achieved by Hydroxypropylation method e.g.; Apios Starches (Mi Hye Park *et al.*, 2020b)**.** Some of the chemical treating agents such as Sodium tripolyphosphate, Sodium meta-phosphate, and sodium acetate have been used in the chemical modification of starch (Mahalia, Supriyanto and Syukri, 2020)**.** The most common approaches to chemical modification for pharmaceutical use include hydrolysis, oxidation, esterification and etherification as shown in the figure 4.

1.5.2.1 Acid hydrolysis

Acid hydrolysis is a substantial chemical modification that may drastically alter the structural and functional characteristics of starch without affecting its granular shape. A thorough understanding of the influence of acid hydrolysis on starch structure and functioning is critical for starch scientific research and industrial applications (Wang and Copeland, 2015). The acid interacts with and depolymerizes the amorphous areas of the granules, causing the granules to rupture fast when the starch is heated above its gelatinization temperature. This results in a hot, lower viscosity cooked starch, when cooked, forms a stronger gel than the original parent starch (Jackson and Ratnayake, 2006). High-amylose starches are resistant to acid hydrolysis, but those with low amylose concentration are quickly hydrolyzed. It has a slower penetration of hydrogen ions into the granules due to their limited swelling (Wang and Copeland, 2015). The acid hydrolysis method has been employed to modify starches such as Chinese yam (*Dioscorea oppositifolia*) and cassava starch, as demonstrated by (Okunlola and Akingbala, 2013 and Mohammed, Isah and Apeji, 2014) respectively, for their applications as binders. Furthermore, studies conducted in Ethiopia have explored the use of Potato (*Plectranthus edulis*) Starch as a directly compressible powder, reported by (Gulla *et al.*, 2020).

1.5.2.2 Oxidation

Oxidation is a type of chemical modification in which carboxyl and carbonyl functional groups are introduced into the starch by successive depolymerization (Hong *et al.*, 2016). It includes the oxidation of the glucose units' primary or secondary hydroxyl groups, resulting in the formation of aldehyde or carboxyl groups. Oxidized starch is created by reacting starch with a specific quantity of oxidizing reagent at a defined temperature and pH of 11.4–12.0 (Kavlani N *et al.*, 2012b). The reaction rates are much quicker than with uncatalyzed hydrogen peroxide (H_2O_2) which is a strong oxidizing agent that can be used for the degradation of various organic compounds, including starch. When hydrogen peroxide is applied to starch, it reacts with the starch molecules by breaking down the glycosidic bonds between the glucose units. This reaction leads to the partial or complete degradation of the starch molecules, depending on the concentration of the hydrogen peroxide and the reaction conditions (Zhang *et al.*, 2016). The repeated application of hydrogen peroxide can be utilized to accurately ascertain the exact degree of degradation.

In comparison to the native starch, the oxidized starch exhibits higher water solubility and reduced viscosity (Emeje, M. and Blumenberg, M., 2020). This approach was used in some studies conducted on Enset (Ensete ventricosum) starch for industrial applications (Zeleke *et al.*, 2019).

1.5.2.3 Substitution

Substituted starches are made by esterifying and etherifying the hydroxyl groups of glucose units, resulting in acetylated starch, carboxymethyl starch (CMS), hydroxyethyl starch, hydroxy propylated starch (Rahaju Maulani *et al.*, 2014), and phosphate starch (Park *et al.*, 2004). The substituted starches are synthesized in aqueous, organic, or water-miscible organic media. Organic media allow for greater substitution, but residues such as by-products and salts are retained in the final products (Hong, Liu and Gu, 2016).

The carboxymethylation of starch is one of the most often used substitution techniques. It involves the reaction of starch with sodium monochloroacetate in the presence of an alkaline catalyst, such as sodium hydroxide. The process causes the hydroxyl groups on the starch molecule to get carboxymethyl groups, which increases the modified starch's negative charges and solubility (Wang *et al*., 2016). The hydroxypropylation of starch is another example of a substitution. In this method, starch is reacted with propylene oxide in the presence of an alkaline catalyst to form hydroxypropyl groups that are then attached to the starch molecule. Acetylation of starch is also good example of substitution technique**,** it is accomplished by reacting starch with acetic anhydride or acetyl chloride in the presence of an acid catalyst, such as hydrochloric acid. As a result of this process, the hydroxyl groups on the starch molecule are changed by the addition of acetyl groups, which increases the modified starch hydrophobicity and thermal stability (Li *et al*., 2015). Several studies have used the substitution method to modify various types of starch, such as potato starch, corn starch, and sweet potato starch in order to improve their physicochemical properties for use as raw materials in industrial applications. For example, carboxymethylation has been used to modify potato and corn starch, resulting in improved solubility, rheological properties, and thermal stability compared to unmodified starch (Singh *et al*., 2007). Similarly, hydroxypropylation has been used to modify sweet potato starch, resulting in improved physicochemical properties (Zhang *et al*., 2014).

1.5.2.4 Cross-linking

The rheological, morphological, and physicochemical properties of starch can be improved by cross-linking, which is widely used as chemical modification method. It involves the use of a cross-linking agent to create covalent bonds between two or more starch molecules, resulting in a network of interconnected starch molecules with improved physicochemical properties. During the cross-linking process, a chemical agent with two or more distinct hydroxyl groups is used to create the covalent bonds

between the starch molecules. The cross-linking agent can have the hydroxyl groups on the same or separate polymer chains as shown figure 3. In contrast to the di- and poly-starch phosphates, which are claimed to be crosslinked, monostarch phosphates are now known to be phosphorylated starches (Mariam *et al*.,2018). The resulting cross-linked starch has improved properties such as increased thermal stability, resistance to shear forces, and reduced susceptibility to enzymatic degradation (Singh *et al*., 2007).

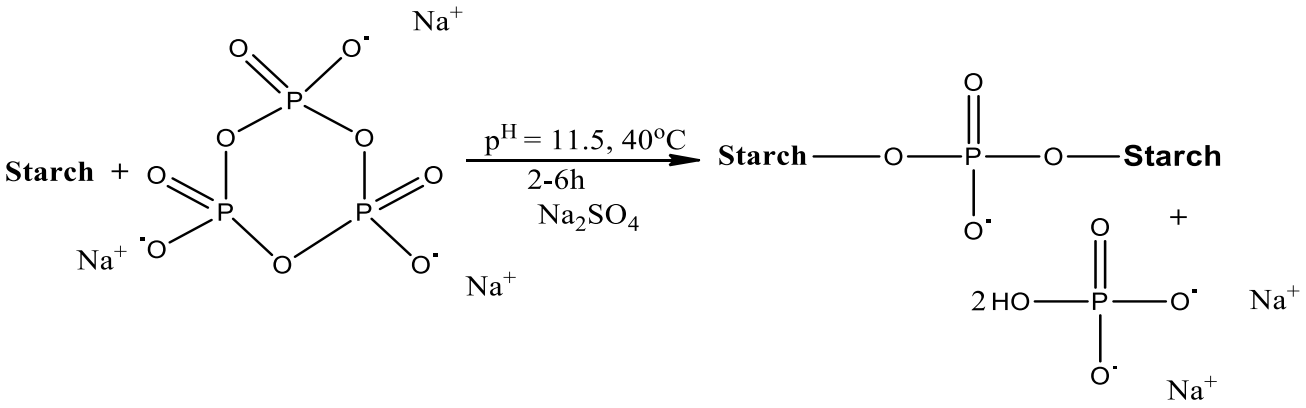


Figure 3: Cross-linking of starch

The amount of chemical reagent required to achieve the required functional properties in the starch may vary depending on the starch source, the type of reagent required for the cross-linking, the degree of cross-linking of the chemical reagent, and the required range of properties in the final modified starch product (S. A. Senanayake *et al.*, 2014). Several chemicals are used to cross-link native starch including sodium Tri metaphosphate (STMP), sodium tripolyphosphate (STPP), epichlorohydrin (ECH), sodium hexametaphosphate (SHMP), and phosphoryl chloride ($POCL_3$), that are used as the primary cross-linking chemicals used to produce cross-linked, food-grade, and medicinal starches (Alcázar-Alay and Meireles, 2015 and Jawad *et al.*, 2013), moreover, due to the cross-linking reaction mechanism and available starch hydroxyls, the type of reagent used and cross-linking conditions determine the ratio of mono and di-type bonds (esters with phosphorous-based agents and glycerol with epichlorohydrin) (Hirsch and Kokini, 1997). The modification of starch through cross-linking has been studied in Ethiopia as a way to develop excipients that can sustain the release of drugs. Two types of starch, specifically Yam (Dioscorea abyssinica) and Enset (Ensete ventricosum (Welw.) Cheeseman), have been examined for their potential as drug release-sustaining excipients (Mulualem *et al.*, 2013 and Tesfay *et al.*, 2020).

Cross-linking can limit or prevent gelatinization and swelling of the starch granules during cooking (Shah, Mewada and Mehta, 2016), even a very low concentration of reagent can cross-link starch, and this is dependent on factors such as starch source, cross-linking reagent composition and concentration, the extent of substitution, reaction time and so on (Shah *et al*., 2016). It has been reported that cross-linking followed by substitution produces starches that are more shear and heat stable than native starch. This could be attributed to a structural change in the granules following the first modification (cross-linking). For example, Starch that was cross-linked first and then hydroxyl propylated displayed lower pasting temperature and viscosity compared to the samples where hydroxyl propylation was done first and then cross-linking (Reddy and Seib, 2000 and Singh, Kaur and McCarthy, 2007). Current study was aimed to address the limitations of native sweet potato starch by modifying it through cross-linking. The modified sweet potato starch was expected to exhibit improved physicochemical properties, including increased thermal stability and making it suitable for a wider range of pharmaceutical applications such as sustained release polymer.

1.5.3 Enzymatic Modifications

The molecular weight distributions of starch macromolecules, as well as the chain lengths of enzymatically modified starches, influence starch properties such as viscosity and texture, revealing the enzymatic processes at work during starch synthesis (Hong, Liu and Gu, 2016). The most frequent enzymes used for this are hydrolyzing enzymes, which produce highly functional derivatives when exposed to starch solutions. This technique's origins may be traced back to the production of glucose syrup or high fructose corn syrup (Kavlani N *et al.*, 2012b). Enzymatic reactions, which take place when the gelatinized starch combines with the given enzyme to generate upgraded starch, can be used to design a starch with a particular and distinctive structure. Amorphous regions of the structure that are less well-ordered are more susceptible to enzymatic replacement, whereas crystalline lamellae are the component of the structure that are most resistant to enzyme treatment (Bhatt *et al.*, 2022).

Enzymatic modification is a commonly used technique for modifying various types of starch, including rice, and corn, starches. Pullulanase, 4-α-glucotransferase, and maltogenic amylase are some of the enzymes used to modify these starches. In addition to these, cassava and potato starches can also be enzymatically modified for various purposes. For example, cassava starch was modified using α-amylase and glucoamylase enzymes, resulting in improved properties such as increased solubility, reduced viscosity, and improved thermal stability. Similarly, potato starch was enzymatically modified

using α-amylase and amyl glucosidase enzymes, resulting in improved properties suitable for use in the pharmaceutical and food industry. Therefore, it is a promising method for enhancing the functional properties of starch (Keshinro *et al*., 2015 and Tavakoli, *et al*., 2016).

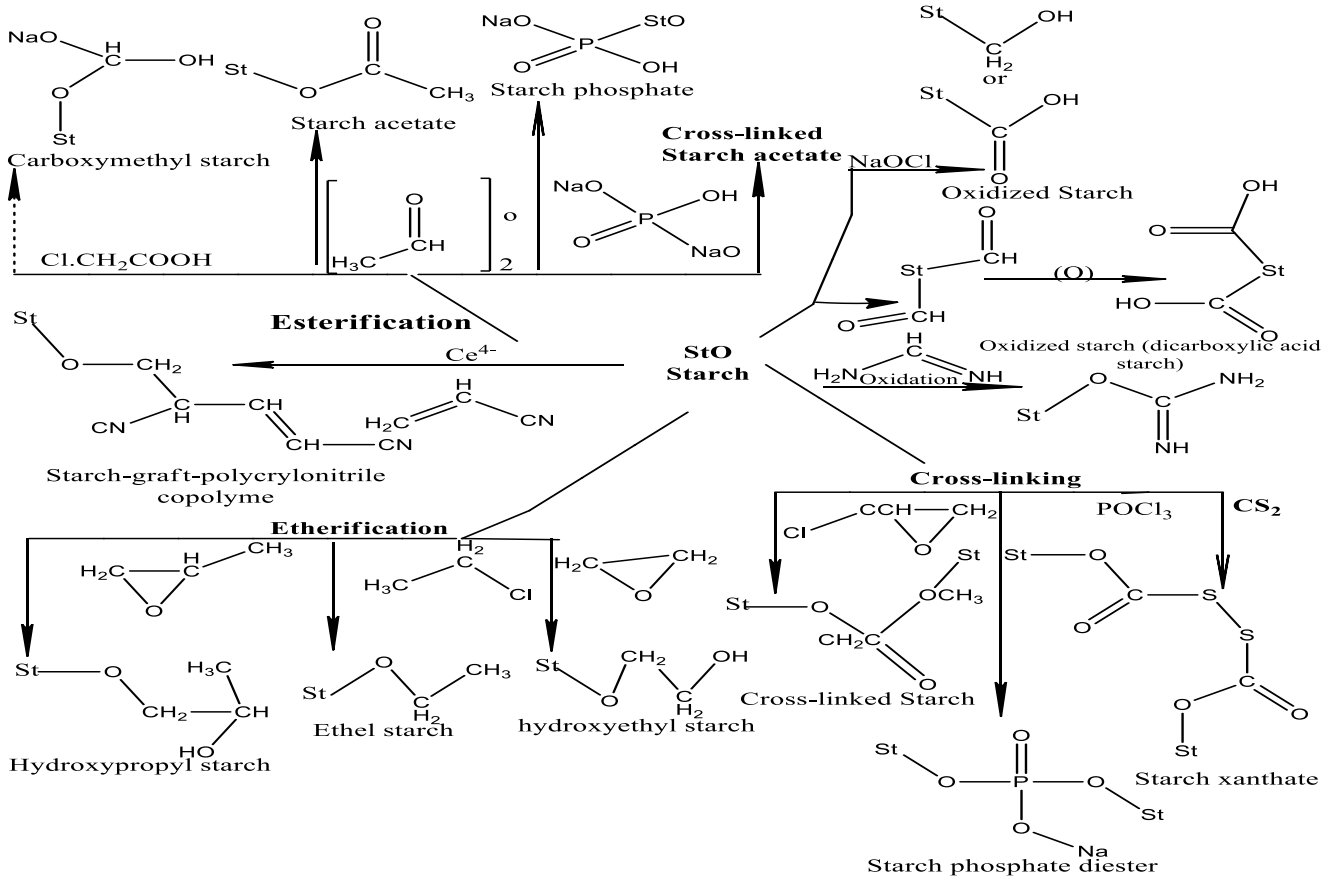


Figure 4: Overview of starch modification methods

1.6 Modified starches in Sustained release formulations

Nowadays, there is a greater emphasis on the development of sustained release because very few drugs are emerging from research, development (Jethara, Patel and Patel, 2015). A sustained-release tablet is a drug product composition that first supplies the needed dosage and then maintains or repeats it at predetermined intervals. They are intended to steadily release the medication after intake. The fundamental reason for the increased usage of these dosage forms is that patient compliance is enhanced and minimize the possibility of missed doses, and plasma drug fluctuations, multiple drug therapy raises the risk of toxicity and raises the overall cost of treatment (Okafo, Avbunudiogba and Ejomafuvwe, 2020 and Goyal *et al.*, 2017).

Biodegradable polymeric materials have been studied extensively as a potential drug carrier for controlled-release applications. Among them, polysaccharide-based microparticles have gained notable attention. This is because they offer flexibility in achieving a desired drug release profile, are cost-effective, and have been widely accepted by regulatory authorities for use in controlled -release drug systems (Liu *et al.*, 2003 and Taylor *et al.*, 2006). Furthermore, polysaccharides demonstrate excellent biocompatibility and biodegradability, both of which are essential properties for polymers utilized as biomaterials. This makes them extensively employed in pharmaceutical formulations, and in numerous cases, they play a critical role in determining the rate of release of the contents of a dosage form (Taylor *et al.*, 2007).

1.6.1 Hydrophilic polymers used in matrix tablets

Matrix tablets are an important tool for controlled and extended drug release among oral products. To prolong and sustain the rate of drug release, the tablet matrix is composed of both hydrophilic polymers and hydrophobic lipids (Mondal, 2018). Hydrophilic polymers are commonly used in matrix tablets as excipients to control the release of active agents from the tablet. In a matrix tablet, the API is uniformly distributed throughout the polymer matrix, which swells upon contact with water, forming a gel network. This gel layer acts as a barrier, controlling the rate of drug release through diffusion through the gel layer (Khan *et al.*, 2022). They have a high affinity for water and can absorb large amounts of it. This property makes them ideal for use in the formulation of controlled-release drug delivery systems such as matrix tablets. Hydrophilic polymers used in matrix tablets include hydroxypropyl methylcellulose (HPMC), Sodium carboxymethylcellulose (NaCMC) and polyethylene oxide (PEO). The use of hydrophilic polymers in matrix tablets has gained significant attention in recent years due to their ability to provide a sustained release of drugs, which can improve patient compliance and reduce dosing frequency. The properties of the hydrophilic polymer used in the formulation of matrix tablets can significantly impact the release profile of the drug and can be tailored to meet specific patient needs (Viridén, Wittgren and Larsson, 2008). However, the selection of the appropriate hydrophilic polymer for a specific drug requires careful consideration of various factors, including the physicochemical properties of the drug, the desired release profile, and the manufacturing process (Singh *et al*., 2017).

In reality, direct compression of the medication, retardant material, and additives results in a tablet with drug particles embedded in the retardant matrix core (Bose Wong, and Singh, 2013). The matrix device creates a matrix (drug(s) mixed with a gelling agent, where the drug is dispersed, the drug is mostly

dispersed within a polymer, and then released by diffusion. The matrix device may be simpler to manufacture and protect against changes in the gastrointestinal tract. The rate of drug release can be influenced by various factors, including food, pH, volume of dissolving media, enzyme concentration, and dietary factors (Rao, N.G *et al*., 2013).

A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. The development of matrix sustained formulations, such as matrix tablets incorporating hydrogels, is now receiving a lot of interest (Li, J. and Mooney, D.J., 2016). The swelling and gelling of the hydrogel, which produces a diffusion barrier and regulates drug release, is the mechanism of drug release from hydrogel-based matrix tablets. Through the channels that the swelling and eroding of the hydrogel generate, the medication is delivered. The formulation of the tablet as well as the hydrogel's composition and concentration may be changed to regulate the release rate (Yu *et al.,* 2021). Several studies on oral extended-release tablets based on starch and its derivatives have been conducted over the last two decades. Many starch-based extended-release excipients have successfully retard drug release (Hong, Liu and Gu, 2016). This research aims to look at a cross-linked sweet potato starch-based excipient in matrix tablets.

1.7 Rationale of the present study

Finding effective and safe excipients for the pharmaceutical industry is a top priority, and the use of polymers as release-retarding matrix components is a common practice. A variety of polymers are available to serve as release retarding matrix components. However, there is still a need for new and improved release-retarding polymers for sustained-release tablets (Chowdary, Mohapatra and Krishna, 2006). The extraction of native starch from edible plant floras, as well as the examination of their chemical contents and physicochemical properties for diverse purposes, including pharmaceutical excipients, have shown to be a good alternative for synthetic polymers (Shit and Shah, 2014), Despite its widespread usage, native starch has several limitations, including low moisture resistance, poor processability, poor mechanical characteristics, and less stability issues in its final products (Majzoobi *et al.*, 2011). As a result, native starch is seldom used directly; instead, starch chemical modification is a well-established method that must be enhanced to overcome those limits (Shah, Mewada and Mehta, 2016).

Sweet potato is one of the potential sources of starch; it is commonly farmed in southern, southwestern, and eastern Ethiopian provinces (Gurmu, 2019). To produce derivatives with improved and specific pharmaceutical raw material, sweet potato starch must be modified. However, no prior research or analysis has been conducted to investigate the effectiveness of chemically modified sweet potato starch particularly by sodium hexametaphosphate as a matrix forming polymer for sustained release (SR) applications. The current study was attempted to chemically modify and evaluate starch from sweet potato for release retarding agent. As a result of the current investigation, one modified natural polymer was produced as a substitute and locally produced and affordable excipient that may be used as a release retarding agent for matrix tablets and meet a requirement in the pharmaceutical sector.

In this study, glibenclamide was selected as a representative drug due to its classification as a biopharmaceutics classification system (BCS) class II drug, which is characterized by low water solubility and high permeability according to the BSC. Glibenclamide is chemically known as 1- [4- [2-chloro-2-methoxy benzamido] ethyl benzo sulphonyl]-3 cyclohexyl urea], and it is considered a weak acid with a pKa value of 5.3. It has a short half-life ranging from 2 to 5 hours, as reported in (Siswanto *et al.*, 2020), and it appears as a crystalline white powder that is sparingly soluble in methylene chloride and methanol and mildly soluble in alcohol and dissolves in weak alkaline solutions (Behera and Sahoo,

2012). As a result, it is a good candidate for formulation in a sustained-release system. Therefore; the aim of this study was to formulate and evaluate matrix tablets of glibenclamide for sustained release.

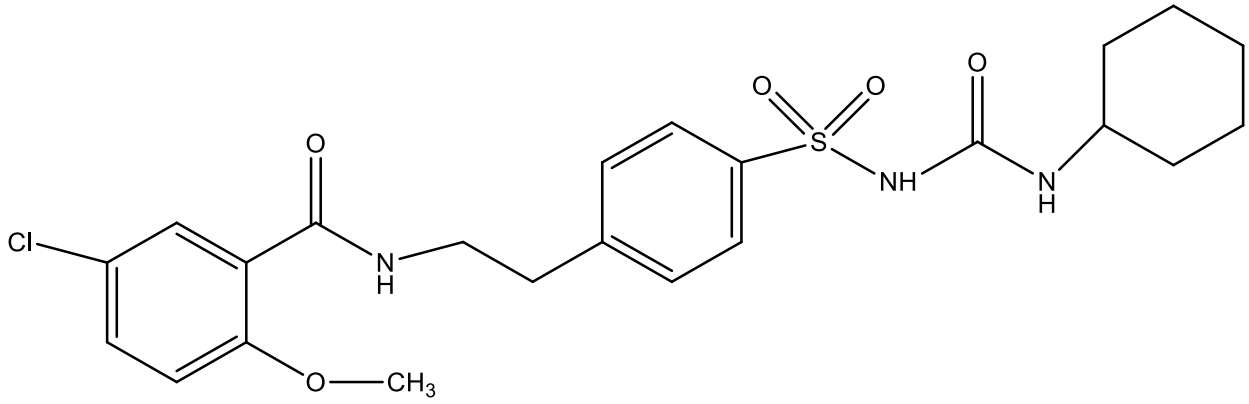


Figure 5: Chemical structure of Glibenclamide (as per Ph. Eur.).

1.8 Research questions

The current study provided answers to the following questions.

1. What are the characteristic properties of cross-linked starch prepared from sweet potato?
2. Can cross-linked (*Ipomoea batatas (L.) Lam*) starch powders be used as Sustained release agents in tablet formulations?
3. What is the release profile of sustained release matrix tablet containing cross-linked (*Ipomoea batatas (L.) Lam*) as release retarding polymer?

2. OBJECTIVES

2.1 General Objective

- ✓ To prepare cross-linked sweet potato (*Ipomoea batatas (L) Lam.*) starch and evaluate its sustained release properties.

2.2 Specific Objective

- ✓ To prepare cross-linked starch from native starch of sweet potato (*Ipomoea batatas (L) Lam.*) and determine the degree of cross-linking.
- ✓ To analyze the physicochemical characteristics of cross-linked starch.
- ✓ To evaluate the tableting and the sustained release properties of the cross-linked starch.

3. EXPERIMENTAL

3.1 Raw Materials and Chemicals

Fresh sweet potato tubers of the Awassa83 variety were collected from the Hawassa Agricultural and Research Center, Sodium metabisulphite and Sodium carbonate (Guangzhou Jinhaunda Chemical Reagent Co. Ltd., Guangzhou, China), Sodium hexametaphosphate (Uni-chem Chemical Reagent Ltd., Wuhan, China), Hydrochloric acid, potassium chloride, and Magnesium stearate (BDH Chemicals Ltd., Poole, England), Sodium hydroxide (Sigma Aldrich, Stockholm, Sweden), Potassium monobasic hydrogen phosphate (Sorensen, Leuren, Germany), Sodium chloride (E. Merk, Stockholm, Sweden) were obtained from the local market. Glibenclamide working standard and Microcrystalline cellulose were generously provided by Cadila and East Africa Pharmaceuticals (Ethiopia) PLC respectively, and Talc, Magnesium stearate and Lactose anhydrous were provided by Ethiopian Pharmaceutical Manufacturing Company S.C (EPHARM).

3.2 Methods

3.2.1 Extraction of starch from sweet potato (*Ipomoea batatas (L). Lam*) tuber

Starch was extracted from the tubers of the sweet potato (*ipomoea batatas (L. Lam*) using the methods developed by Gebre-Mariam and Schmidt, (1996), Zhu *et al.*, (2011) and Cepeda *et al.*, (2016), with minor modifications. About 20 Kg of fresh tubers were cleaned, peeled, and chopped into little pieces, then milled in a local pulverizer with small quantities of distilled water. The resulting slurry was then suspended overnight in extra distilled water including 0.075 % (w/v) sodium metabisulphite (SMBS), the mass was then pressed via layers of muslin, and the resulting filtrate was allowed to settle overnight, the supernatant was decanted after the suspension had sedimented, and the sediment starch was redispersed and washed with another 0.075% (w/v) SMBS solution till the supernatant was clear, neutral in P^H, and freed from any soluble material. Finally, the starch was allowed to dry in the open air for 2 days before being grinded to a fine powder in a mortar and pestle, then sieved with a 224-mesh size sieve, and stored in a completely sealed container under dry condition.

3.2.2 Preparation of Cross-linked Sweet Potato (*Ipomoea batatas (L). Lam*) Starch

Sweet potato starch was cross-linked using a specific method with minor adjustments (Wang *et al.*, 2021). To begin, 100g of sweet potato starch (dry basis) was dispersed into distilled water (200 ml) containing bakers and stirred magnetically at 50 °C for 10 minutes. The starch slurry was adjusted to

pH 11 with 1 M of NaOH solution. The cross-linking reagent: sodium hexametaphosphate (SHMP) was added dropwise in different concentrations (10%, 15%, and 20% w/w), then 2 g of Na_2CO_3, 5 g of NaCl were added to on each slurry mixture and the mixtures were stirred continuously at 55^oC for 8 hours on the water bath (Memmert GmbH & Co. KG). After the reaction time was completed, the starch suspension (slurry) was adjusted to pH 6.5 with 1 M of HCl solution to terminate the reaction, then washed three times with deionized (distilled) water and filtered by using grade -2 filter paper in a Buchner funnel and dried at 50 ^oC for 48 hours in free air and then powdered it using a laboratory mortar and pestle, sieved with a 224-μm mesh sieve, and finally packaged in an airtight container.

Table 1: The reaction condition for cross-linking of native sweet potato starch with three different concentrations of sodium hexa-metaphosphates

CLSPS Types	SHMP (%, w/w)	NaOH% (w/w)	Na_2CO_3%, (w/w)	NaCl (%w/w)	Reaction time (h)	Reaction temperature ^0C
10%-CLSPS	10	1M	2	5	8	55
15%-CLSPS	15	1M	2	5	8	55
20%-CLSPS	20	1M	2	5	8	55

3.2.3 Physicochemical characterization of cross-linked starches

3.2.3.1 Determination of peak viscosity

The peak viscosity of the cross-linked sweet potato starches (CLSPS) and native samples were measured using a rotary viscometer (electrometer, 2300RV1L, IP20, Spain) with Spindle number 4 at shearing stress of 100rpm. As a method explained with a little adjustment (Jayakody *et al.*, (2007), and Jawad *et al.*, 2013). Starch suspension containing 10% (w/v) starch were prepared and shaken for 3 minutes. The suspension was then heated in a water bath from 50 to 90^oC, while their peak viscosities were measured at 50, 70 and 90^oC of using the viscometry digital display. The peak viscosities of the same sample were recorded when they were cooled from 90^oC to 50^oC after being kept at 90^oC for 5 minutes. The greater peak viscosities over the whole heating - cooling cycle was recorded and used to calculate the degree of cross-linking (DCL) in CLSPS samples. Viscosities recorded are averages of three determinations and standard deviation.

3.2.3.2 Determination of Degree of Cross-linking (DCL)

The viscosity values were used to compute the DCL of modified starches, and it was calculated using the equation (3.1)

$$DCL = \frac{(A-B)}{A} \times 100 \quad \text{..... Equation (3.1)}$$

Where A represents the peak Viscosity of NS and B represents peak Viscosity of the CLSPS at temperature of heating and cooling cycle, the results were calculated as a mean of three independent measurements.

3.2.3.3 *Solubility and Swelling Power*

The solubility and swelling power of native and cross-linked sweet potato starch in water at different temperatures were determined according to the method described in (Lerd luksamee *et al.*, (2013) and Gulla *et al.*, (2020) with minor modifications. A, 0.5g sample of starch (wi) was added to a pre-weighed centrifuge tube along with 10ml of distilled water. The suspensions were shaken for 4 minutes before being heated in a thermostatically controlled water bath (ZENITH LAB, HH-W420HH-W600, Jiangsu, China) for 30 minutes at temperatures ranging from 25ºC to 95ºC, then continued shaking at every 4 minutes. After heating, the suspensions were allowed to cool to room temperature and then centrifuged at 3000rpm for 15 minutes to separate the gel (Wg) and supernatant. The supernatant was carefully decanted and dried in an oven (Kottermann®2711, H. JURGENS & CO., Bremen, Germany), at 130°C for two hours to obtain the residue (Ws) which was weighed to determine the quantity of starch solubilized in water at that temperature. All experiments were carried out in triplicate to ensure that the results were precise and consistent. The calculation of the solubility and swelling power of starch in water at various temperatures was based on the following equations:

$$\text{Solubility (S\%)} = \frac{Ws}{Wi} \times 100 \quad \text{.....Equation (3.2)}$$

$$\text{Swelling power (w/w\%)} = \frac{Wg \times 100}{Wi(100 - S(\%))} \quad \text{..... Equation (3.3)}$$

Where: Wg is weight of separated gel. Ws is the weight of solubilized starch. W_i is initial weight.

3.2.3.4 Determination of Moisture content

The moisture content was determined according to the method used by (Gebre-Mariam and Schmidt, 1996). To begin the experiment, a precise amount of 2g of starch was carefully weighed and transferred into a pre-weighed and dry Petri-dish. The Petri-dish was then placed inside a hot air oven (Kottermann® 2711, Germany) and heated for a period of 4 hours at a constant temperature of 130°C. After the heating process was completed, the final weight of the Petri-dish and its contents was recorded for further analysis. Equation 3.4. was used to compute the moisture content, and the results were calculated as the mean of three triplicates.

Moisture Content = $\frac{(Wi - Wf)}{Wi} \times 100$ ……..……...Equation (3.4)

Where Wi and Wf are initial and final weights starch after heating respectively

3.2.3.5 Moisture sorption pattern

Moisture sorption characteristics were determined using the method (Odeku and Picker-method. 2009), with minor modifications. 5 grams of each sample were dried in oven (Kottermann® 2711, Germany) at a temperature of 120°C for a duration of 4 hours. The dried samples were then evenly spread on pre-dried and weighed petri dish plates. These plates were then transferred to Pyrex desiccators, which contained a suitable solvent, set to specific relative humidity levels of 11%, 20%, 40%, 75%, 85%, and 100%. The samples were left to equilibrate for four weeks at room temperature. After the recommended time, the moisture absorption of each sample was determined by calculating the difference in moisture content before and after equilibration (Tesfay *et al.*, 2020).

3.2.3.6 Determination of Bulk (ρBulk) and tapped densities (ρTapped)

Bulk density

The bulk density of native and cross-linked starches was measured by taking 60 g of powder and carefully pouring it into a 250 ml graduated glass measuring cylinder. The cylinder was then tapped gently to ensure that all the powder stuck to the walls of the cylinder was collected. The volume recorded directly from the cylinder was used to calculate the bulk density. Equation 3.5 was used to get the bulk density (g/cm^3). The final result was calculated as the average of three measurements.

$$\rho b = \frac{W}{Vb} \text{……..……...……Equation (3.5)}$$

Where;

ρb: Bulk density (g/cm^3), W: Mass of powder (g), $V_{b:}$ Bulk volume of the powder (cm^3)

Tapped density

To estimate the tapped powder densities, a tap densitometer (ERWEKA, SVM 20, Germany) was used. A 60 g powder sample was carefully transferred into a 250 ml graduated cylinder and tapped 500 times. The tapped volume was then recorded, and Equation. 3.6 was used to estimate the tapped densities.

$$\rho t = \frac{W}{Vt} \text{ ……..……..……...……. Equation (3.6)}$$

Where;
ρt = Tapped density(g/cm^3)
W = Mass of powder(g)
V_t = Tapped volume of the powder (cm^3)

3.2.3.7 The Carr"s index (compressibility) and Hausner ratio

The powder properties were determined by calculating the values using Equations 3.7 and 3.8, which were based on the bulk and tapped densities of the sample. The calculated values were obtained after conducting three determinations.

$$Carr\ '\ s\ index\ \% = \left(\frac{\boldsymbol{\rho t - \rho b}}{\boldsymbol{\rho t}}\right) x100\% \quad \text{Equation (3.7)}$$

$$Hasner\ Ratio = \left(\frac{\rho t}{\rho b}\right) \quad \text{Equation (3.8)}$$

Where: ρ_b is bulk density and

ρ_t is tapped density of starch samples.

3.2.3.8 Angle of repose

The fixed height funnel method was employed to measure the angle of repose and flow rate of the powders. 60 grams of powder were forced to flow through a stemless funnel with an internal aperture diameter of 10 mm at the bottom and 100 mm at the top. The funnel was positioned at a height of 10 cm from the tip to the base. The diameter (d) of the pile as well as its height (h) were both measured. Then, using Equations 3.9 angle repose (θ) was determined respectively.

$$\boldsymbol{\theta = Tan^{-1}\left(\frac{h}{r}\right)} \quad \text{Equation 3.9}$$

Where: h: height

θ : angle of repose and

r: radius

3.2.4 Drug–Starch compatibility study

3.2.4.1 Fourier Transformed- infrared spectroscopy (FT-IR) Analysis

To test for compatibility, the glibenclamide drug, 20%-CLSPS, and 1:1 Physical combination were subjected to Fourier Transform Infrared Spectrophotometer (FT-IR) *(Model-perkin Elmer, USA)* analysis after one week of storage. Prior to analysis, the samples were ground using a mortar and pestle to reduce the average particle size. The FT-IR analysis involved placing an adequate amount of drug and physical mixture powder sample onto an infrared spectrometer disk. The sample was then scanned in the range of 4000–450 cm^{-1} using a spectrophotometer, and the spectra were obtained (Bose, Wong and Singh, 2013).

3.2.4.2 DSC Thermal Analysis

To determine the interaction of excipients with the drug, differential scanning calorimetry (Mettler Toledo, DSC20, China) was performed. The sample was precisely weighed onto aluminum pans, which were then hermetically sealed with aluminum lids. Thermograms were obtained in a liquid nitrogen environment (flow rate 10ml/min) at a scanning rate of 10°C/min over a temperature range of room temperature to 400°C. To investigate the drug-polymer interaction, the DSC of a physical mixture of glibenclamide and 20%-CLSPS was recorded (Youssef *et al.*, 2021).

3.2.5 X-ray Diffraction Studies (XRD)

3.2.5.1 Determination of crystallinity nature of starch

Powder X-ray diffraction data were measured using a Rigaku MiniFlex 600 powder X-ray diffractometer (Rigaku, Tokyo, Japan) equipped with Cu Kα radiation (λ = 1.5406 Å, Ge monochromator). The analysis was conducted using a medium scanning mode, operating at 40 kV and 40 mA, with a Bragg angle 2 θ ranging from 5^o to 60^o and a 0.01^o steps size or sampling interval. The crystallinity of the native and two cross-linked starches was determined by analyzing the major diffraction peaks, using Origin Lab Pro-2016 64-bit software based on the method described (Cheetham and Tao, 1998).

3.2.6 Studies of thermal properties

3.2.6.1 Thermogravimetric Analysis (TGA) and Differential Thermal Analysis (DTA)

Differential Thermal gravimetry (DTA-60H, Japan) was used to perform thermogravimetric analysis for determining the thermal stability of starches by measuring both the weight loss of the sample as it is heated and the difference in temperature between the sample and a reference material as the sample is

heated or cooled. The water loss was calculated after heating the powder at a rate of 10 K/min from 20 to 800^{o}C (Odeku and Picker-Freyer, 2009). All analyses were carried out in triplicate

3.2.7 Particle size and surface morphology studies

3.2.7.1 Particle size and size distribution

Particle Size, Size distribution and the specific surface area of the starch sample ware measured with a laser diffraction system (Mastersizer 2000, Malvern Instruments, Worcestershire, U.K.) equipped with a small volume sample dispersion unit (Hydro 2000SM). A small amount of starch powder was dispersed in 400ml of Millipore water in a sampler by stirring at 1500 rpm until an obscuration of 10–30% was noted, and the measuring time was 5 sec. Particle size distribution homogeneity and volume and surface weighted means diameter (μm) were calculated. The results given are the average values of three measurements (Schmidt and Germany, 1998).

3.2.7.2 Scanning Electron Microscopy (SEM)

SEM was used to examine the surface morphology of native, and the cross-linked sweet potato starches. The samples were mounted on alumina stubs, coated with gold in a Hitachi HUS-GB vacuum coating unit, and observed with a scanning electronic microscope at a voltage of 10Kv. Image obtained from SEM to determine the differences in surface morphology between the native and modified starch samples.

3.2.8 **Tablet preparation**

3.2.8.1 Formulation of Glibenclamide Sustained Release Matrix Tablets

Sustained release glibenclamide (GLB) matrix tablets were prepared by using the direct compression method. The CLSPS was used as a release retardant polymer, microcrystalline cellulose (MCC) Avicel PH 102- was used as a diluent and directly compressible excipient, and a 2:3 ratio of magnesium stearate and talc were used as lubricant and glidants respectively. The matrix formulation consisted of 10 mg GLB along with varying proportions of native and cross-linked starch (10%-CLSPS, 15%-CLSPS, and 20%-CLSPS), as detailed in Table 2. To ensure homogeneity, GLB and all other ingredients were sieved individually and blended them in a turbine mixer for 10 minutes, followed by an additional 5 minutes after adding lubricant. Finally, an 8-station rotary compression system with 7.5 mm concave punches was used to make matrix tablets with a mean weight of 200 ± 10 mg (Ramteke *et al.*, 2019).

Table 2: Composition of GLB matrix tablets 200mg with different proportion of CLSPSs.

Sr. No	Ingredients in mg/tab	Formulation code									
		F_{NS}	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
1	**Glibenclamide**	10	10	10	10	10	10	10	10	10	10
2	**NS**	140	--	--	--	--	--	--	--	--	--
3	**10%-CLSPS**	--	100	120	140	--	--	--	--	--	--
4	**15%-CLSPS**	--	--	--	--	100	120	140	--	--	--
5	**20%-CLSPS**	--	--	--	--	--	--	--	100	120	140
6	**MCC**	20	50	40	30	50	40	30	50	40	30
7	**Lactose anhydrous**	25	35	25	15	35	25	15	35	25	15
8	**Talc**	3	3	3	3	3	3	3	3	3	3
9	**Mg stearate**	2	2	2	2	2	2	2	2	2	2
10	**Total weight(mg)**	200	200	200	200	200	200	200	200	200	200

NS: Native sweet potato starch, MCC: Microcrystalline Cellulose, Mg stearate: Magnesium Stearate, CLSPS -Cross-linked Sweet Potato Starch with 10,15 and 20% of sodium hexametaphosphate (SHMP) respectively.

3.2.9 **Tablet evaluation**

3.2.9.1 Thickness

The thickness of ten matrix tablets was measured using a sliding vernier caliper (Nippon Sokutei, Japan). The mean values with standard deviations are reported as the results.

3.2.9.2 Crushing strength and diameter

The crushing strengths and diameters of ten tablets from each batch were assessed using a Tablet Hardness Tester (ERWEKA TBH220D, Germany). Each tablet was put between two anvils, and the crushing strength that caused the tablet to break and its diameter were recorded. The average and standard deviation of the data were calculated.

3.2.9.3 Tensile strength

The radial tensile strength (σ) for crushing (T) was calculated using the equation (3.13):

$$\sigma = 2F/\pi . D . T$$ ……...……...……...……...Equation (3.13)

where; F is the force required to break the tablets, D and T are the diameter and thickness of the tablets respectively.

3.2.9.4 Weight Uniformity

Twenty tablets were randomly selected from each batch and weighed (Wi) using an analytical balance (OHAUS AR3130, China). The resulting average weight (W_a) was then calculated. The percent weight variation was determined by applying equation 3.14, and the acceptable criteria were employed based on the guidelines specified in USA Pharmacopeia.

$$\textit{Weight variation (\%)} = \left(\frac{Wa - Wi}{Wa}\right) 100 \quad \text{Equation (3.14)}$$

3.2.9.5 Friability

To determine the friability of each formulation, a sample of twenty tablets was randomly selected and weighed precisely (W_I). The tablets were then subjected to abrasion using a tablet friability tester (Roche friabilator (ERWEKA, TAR 20, Germany)) at a rotational speed of 25 rpm for 4 minutes. The tablets were reweighed (W_F), and the difference in weight was calculated as a percentage. The following formula was used to determine the friability:

$$\textit{\%Friability} = \frac{[WI - WF] \text{ X } 100}{WI} \quad \text{Equation (3.15)}$$

It is not permitted to lose more than 1% of the weight of the tablets being tested.

3.2.9.6 Disintegration time

The disintegration time was determined according to the United States Pharmacopoeia's disintegration test for uncoated tablets (USP 30/NF25, 2007). Disintegration apparatus (ERWEKA GmbH, Heusenstamm, Germany) was used to test six tablets at a time, with the immersion fluid being a 0.1N HCl solution kept at 37$\pm$2 ^{0}C. To determine the average disintegration time and standard deviation, it is essential that particles from all tablets pass through the wire mesh without any remaining intact mass on the mesh.

3.2.9.7 Content Uniformity Test

The drug content of ten tablets from each batch of formulations was evaluated by weighing, and individual tablets were placed in a 50-ml volumetric flask containing 5 ml of methanol and small amount of buffer solution then mixed with the aid of ultrasonicate until fully dispersed and diluted with an intestinal simulated fluid without enzyme phosphate buffer (pH 7.4). Then 10 ml was taken and further diluted with the respective solution to make a 50 ml solution. These samples were then filtered, their absorbances measured with a UV-1600 PC Spectrophotometer at wavelengths of 228 nm, and the

contents were compared to a calibration curve established with standard GLB in the same medium ('USP30-NF25 (1) (2)', 2007).

3.2.10 **Standard Curve of GLB in HCI solution at pH=1.2 and in phosphate buffer solution**

3.2.10.1 Preparation of working Solution

To make a 100 µg/ml working solution, 10 mg of the GLB working standard was carefully weighed and placed in a 30 ml beaker containing 10 ml of methanol, which was then sonicated for 10 minutes. The solution was then transferred to 100 ml volumetric flasks, which were adjusted with a phosphate buffer solution at a pH of 7.4 and an HCl solution at a pH of 1.2, respectively.

3.2.10.2 Selection of Wavelength

A UV-1600 PC spectrophotometer was used to run the working solution of GLB 100 µg/ml prepared in both buffer solution at pH 1.2 and 7.4 in the region of 200–400 nm with a medium scanning speed. The solutions maximum absorbance ((λmax) was obtained at 228 nm; thus, the λ_{max} is utilized in the next steps. To accomplish the linearity and calibration curve of the proposed technique, the absorbance of serially diluted aliquots of GLB was measured at 228 nm. In addition, statistical measures of the y-intercept and regression correlation were calculated by the side of the linearity graph for the confirmation of Beer's Lambert law.

3.2.11 ***In-vitro* dissolution study**

The release profiles of GBL from matrix tablets were examined in two different buffer solutions to mimic the various physiological fluids in GI-tracts. The pH 1.2 buffer solution represented the gastric condition, while the pH 7.4 buffer solution simulated intestinal fluid. The dissolution process was conducted using USP Type-I dissolution equipment (rotating basket apparatus-1) with 900 mL of the dissolution medium, pH 1.2, and the test was done for 2 hours, then continued for the next 10 hours after changing the dissolution media with a pH 7.4 buffer solution. The basket speed was set at 75 rpm, and the dissolution medium temperature was maintained at 37^0C $\pm$0.5°C. The device was turned on, once the tablets were put in the dissolution medium. At specific intervals (0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9,10, and 12hour), the samples (each 10ml) were taken and replaced with 10 ml of fresh dissolution medium, which was kept at the same temperature to maintain sink condition. Whatman filter paper No-41 was used to filter every 10 ml of withdrawal sample solution, which was then estimated for drug absorbance at 228nm using (UV-1600PC) UV-visible spectrophotometer. Finally, the corresponding drug content

in the samples was calculated from the calibration curve of GLB to determine the drug release pattern (Nayak *et al*., 2016).

3.2.12 **Analysis of drug release kinetics**

The release kinetics of all batches were studied using various models including Zero-order, Hixson-Crowell, Higuchi Matrix

Higuchi Matrix model, and Korsmeyer Peppa's model to determine the best fit.

i. Zero order kinetics

The sequence and distinct release methods of several types of controlled release formulations are thought to be imparted by drug release kinetics. The release of the drug from dosage forms is achieved in a controlled and gradual manner, as demonstrated by the following equation. Zero order (Cumulative percentage of drug release verses time)

$Q_t = Q_0 + K_0t$……..……...…….. Equation (3.16)

Where, Q_t = the fraction of drug released in time

Q_0 = Initial amount of drug in the tablet, K = Rate Constant t = Time

ii. Hixson-Crowell model

The Hixson-Crowell model describes the release from systems where there is a change in surface area and diameter of particles or tablets. Hixon-Crowell model (cubic root cumulative percentage of drug release versus time).

$Q_0^{1/3} – Q_t^{1/3} = K_{HC}.t$……..…… Equation (3.17)

Where,

Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is Hixson-Crowell. The plot made: cube root of drug % remaining in matrix vs. time (Hixson-Crowell model)

iii. Higuchi matrix model

This model assumes that drug release from a matrix system is controlled by diffusion of the drug through the matrix, and that the surface area of the matrix remains constant during drug release. Higuchi model (cumulative percentage of drug release versus square root of time).

$Q_t = K_H.t^{1/2}$……..…… Equation (3.18)

Where, Q_t = Amount of drug released at time ‘t’, K_H is the Higuchi dissolution rate constant

iv. Korsmeyer-peppas model

This model assumes that drug release from a polymeric matrix system is due to a combination of Fickian diffusion and non-Fickian mechanisms such as swelling and erosion. The equation for this model is Kors Meyer model (log cumulative percentage of drug release versus log time).

$M_t / M\infty = K.t^n$……..……...…….…… Equation (3.19)

Where, Mt/M∞ is the fraction of drug released at time t, M∞ is the total amount of drug in the matrix

K = constant incorporating structural and geometric characteristics of the drug dosage form.

n = diffusional exponent for the drug release as described in Table 3.

Table 3: Diffusion exponent and drug release mechanism for various systems

Diffusion exponent (n)	Diffusion exponent
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-ll transport
n>0.89	Super case-ll transport

3.2.13 Statistical analysis

The data obtained was statistically analyzed to compare individual differences through analysis of variance, on SPSS 23 software with a confidence interval of 95%, and any P-values less than 0.05 were considered statistically significant. The results were presented as the mean value ± standard deviation. To create the figures and graphs for the results obtained from the instrumental analysis, the Origin 8.5.1 software (OriginLabTM Corporation, USA) was employed.

4. RESULTS AND DISCUSSION

4.1 Preliminary studies

The preliminary study aimed to select the optimal reaction conditions, and amount of cross-linking agent for preparing CLSPS with high DCL. In order to establish a starting point for tablet formulation using direct compression, a minimal amount of cross-linked starch was employed as a baseline. To ensure the accuracy and reliability of the analytical method used, the method validation was conducted according to ICH guideline Q2 (R2). Various parameters, such as specificity, linearity, precision, and robustness, were evaluated during the validation. The results of the validation confirmed the suitability of the method for the intended purpose and provided confidence in the quality of the data obtained.

4.2 Characteristics of cross-linked starches

4.2.1 Rheological properties

The result presented in Table 4 shows that the viscosity characteristics of cross-linked sweet potato starch samples decreased as the heating temperature and concentration of cross-linking agent increased. The samples were ranked in order of decreasing viscosity as follows: Native starch > 10%-CLSPS > 15%-CLSPS > 20%-CLSPS notably, the viscosity of the native starch was higher than that of the modified samples. The peak viscosity measurements of both cross-linked (CL) and native starches ranged from 750.34± (11.44) to 3326.6± (98.0) cP. These results suggest that native starch is more susceptible to change in temperature during heating and cooling processes. Statistical analysis revealed that there were significant differences ($P < 0.05$) in the peak viscosities of both native and cross-linked starches (CLSPSs) suspensions. Specifically, at the end of heating and cooling cycle, which was at 50^{o}C, the peak viscosity of the native starch was found to be higher than that of the cross-linked starch. These finding suggests that the native starch was less resistant to heat changes that typically inhibit pasting (Femi-Oyewo, Ajala). The peak viscosity (PV) of the cross-linked starches showed an inverse relationship with the concentration of sodium hexametaphosphate (SHMP). Specifically, the PV values increased as the SHMP concentration decreased, with the highest PV values observed for the starches cross-linked using lower SHMP concentration. However, the PV gradually decreased as the SHMP concentration increased up to 20%. This indicates that the presence of the crosslinking agent would result in lower peak viscosity values by reducing the interactions of starch molecules with water molecules (Yai, 2014). These results are consistent with previous studies Shah, Mewada and Mehta, (2016) which reported that a higher level of crosslinking in starch results in a lower peak viscosity.

Moreover, a higher density of cross-links within starch granules, which can consistently decrease the swelling behavior of starch and strengthen the starch granules' structural integrity and slow down the breakdown of hydrogen bonds during the gelatinization process, resulted in low viscosity (Bruni *et al.*, 2018). As table 4 shows the results of an experiment carried out on spindles No. 4 using 10% w/w starch suspension at different temperature, with a constant RPM of 100.

Table 4: Peak viscosity of native and CLSPS during heating–cooling cycle.

Samples	***Peak viscosity in (cP) of increasing temperature in ^oC***			***Peak viscosity in (cP) of decreasing temperature in ^oC***		
(^OC)	**50**	**70**	**90**	**90**	**70**	**50**
NS	1370±35.59	1486. 6±64.5	2116.6±79.3	2420±64.80	3240±170.50	3326.6±98.0
10%-CLSPS	1343.3±84.9	1553.33±127	1340±165.73	1440±228.60	1150±102.30	1073.3±61.8
15%-CLSPS	1080±114.3	1340±57.15	877.5±76.28	860±190.960	843.33±68.47	820±29.60
20%-CLSPS	1141.34±41.8	1052.3±46.1	967.6±16.5	919.6±11.1	832.4±10.6	750.34±11.44

Parenthesis represents ± SD (standard deviation), n: number of measurements. n=3, $_C$P = centipoise. **Note** that 1 mPas is equivalent to 1 cP. The data presented (Mean ± SD, n=3)

In addition, previous studies have reported similar findings regarding the reduction in viscosities of cross-linked rice and maize starch with increasing sodium Tri metaphosphate (STMP) content (Gao *et al.*, 2014). Another study found that higher phosphorus concentrations can lead to lower peak viscosity values, which might be attributed to phosphorus cross-linking bonds created between and within starch molecules (Liu and Yan, 2018). As stated by Sukhija, Singh and Riar, 2015, cross-linking strengthens the starch granules, making them more heat- and shear-resistant, which can result in a decrease in the viscosity of modified starches. The formation of complex amylose-lipid compounds can weaken the starch granule structure and inhibit starch swelling, ultimately leading to a reduction in viscosity (Oktaviana, D. and Saepudin, E., 2021).

4.2.2 Degree of cross-linking

The effect of cross-linking agents is mainly associated with the degree of cross-linking (DCL) (Siroha, Punia and Sandhu, 2021). The DCL in starch is influenced by several factors such as the type and concentration of the cross-linking agent, temperature, reaction time, pH, and other conditions related to the treatment of starch. These parameters play a crucial role in determining the degree of cross-linking

in starch (Shah, Mewada and Mehta, 2016). In Table 5, there is a comparison of the DCL starches that have been cross-linked at three different levels. The DCL in the cross-linked starches varied between 67.73 to 77.57%. The highest degree of cross-linking was observed in the starch modified with 20% sodium hexametaphosphate. It has been observed that the DCL is lower for starches that have been cross-linked at 10% and 15% levels. This suggests that there is a relationship between the concentration of the cross-linking reagent and DCL. Starches treated with higher concentrations of the reagent and at higher temperatures showed greater cross-linking, while those treated with lower concentrations and temperatures exhibited less cross-linking (Jawad *et al.*, 2013). Moreover, the peak viscosity of starches gradually lowered while the degree of cross-linking increased as concentrations of SHMP increased. Cross-linked starch treated with 10, 15, and 20% of SHMP, exhibited DCL values of 67.73% ± (1.86), 75.35% ± (2.99) and 77.45% ± (0.34) respectively. These findings suggest a positive correlation between the concentration of the cross-linking reagent and DCL in the starch. The obtained results were consistent with a previous study conducted on barley starch by (Malekpour et al, 2016). Similar observations were also reported by Singh *et al.*, (2021) on cross-linked Sorghum starch and rice starch using different epihydrochloride concentrations as a cross-linking reagent showed that increasing the concentration of the cross-linking agent by 0-10% resulted in a higher degree of cross-linking (Koo, Lee and Lee, 2010). In current study, a high DCL achieved with maximum cross-linked starch was 75.35 %. The effect of cross-linking on starch can vary depending on the starch source and cross-linking agent used (Agric and Article, 2019). It is important to consider these factors when optimizing starch modification

Table 5: Peak viscosities at end temperature 50^{o}C and DCL of cross-linked sweet potato starch

CLS Samples	***Peak Viscosity (cP))*** (Mean ± SD, n=3)	***Degree of Cross-linking (%)***(Mean ± SD, n=3)
NS	3326.6±98.0	©
10%-CLSPS	1073.3± 61.8	67.73% ± 1.86
15%-CLSPS	820± 29.690	75.35% ± 2.99
20%-CLSPS	750.34± 11.44	77.45% ± 0.34

NS: Native starch, 10%-CLSPS15%-CLSPS, and 20%-CLSPS represent cross-linked sweet potato starch with 10%, 15%, and 20% of sodium hexametaphosphate. © represent no data.

4.2.3 Solubility and Swelling power

The solubility and swelling power of native and cross-linked sweet potato (CLSPS) are shown in figures 6 and 7 respectively. The solubility and swelling power values of the CLSPS samples fell within the

range of 2-14% and 2.37-13.6 g/g, respectively. The solubility and swelling power values of the CLSPSs were significantly lower ($P < 0.05$) than those of the native starch, which had a solubility of 18.9% and a swelling power of 38.0 g/g. These values of native starch were generally low at low temperatures (25 °C) but increase as higher temperatures, possibly due to the formation of hydrogen bonds between water molecules and hydroxyl groups in amylose and amylopectin units (Paixão e Silva *et al.*, 2021). This observation is consistent with the findings of Olayinka and Adebowale, (2013) which reported that solubility and swelling power of native starch were typically modest at low temperatures but increased considerably at 95°C. According to Thys *et al.*, (2013) the increase in swelling power is due to the breaking of intermolecular hydrogen bonds in amorphous regions of the starch molecule, which allows for progressive water absorption. Additionally, increased kinetic energy at higher temperatures also facilitates solvent accessibility (Tsui and Case, 2000).

However, swelling and solubility of CLSP starch were significantly decreased evidently as the DCL increased. This finding is consistent with studies conducted by Meifang, Yunyun and Qunyu, 2019, which stated that interactions between functional groups of starch cause the creation of stiff clusters of highly organized amylopectin side chains, which leads to decreased swelling power. Additionally, the lower swelling power of cross-linked starches can be attributed to the creation of more jelly mass, which restricts the access of water into starch. Moreover, according to the report (Ibikunle *et al.*, 2019), cross-linking strengthens granule structure and limits water absorption by restricting starch chain movement in the amorphous region, and granules will remain intact due to the chemical bridges. It is well understood that cross-linked starch granule strengthens the hydrogen bonds that hold the granules together, resulting in restricted swelling of the granules during gelatinization, the degree of which is proportional to the amount of cross-linking agent used (Kim and Yoo, 2010 and Shah, Mewada and Mehta, 2016).

Cross-linked (CL) starch is less disintegrated due to high density which is responsible for the decrease in solubility (Siroha, Punia and Sandhu, 2021), not only that but also it can limit the hydration of the gel's hydroxyl groups caused by the increased number of interchain bridges introduced by higher DCL causing swelling power to decrease as SHMP concentration increases (Benjun *et al.*, 2020).

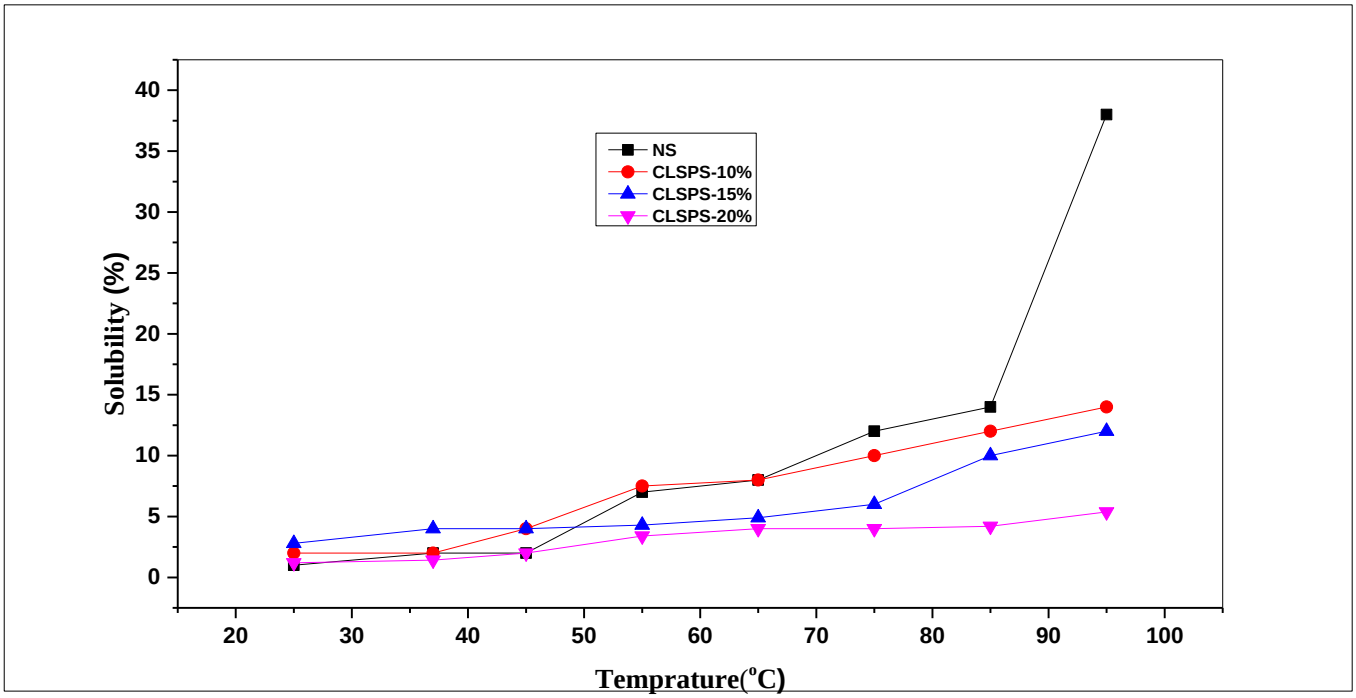


Figure 6: Solubility of native and CLSPS (cross-linked sweet potato starch) at different temperatures.

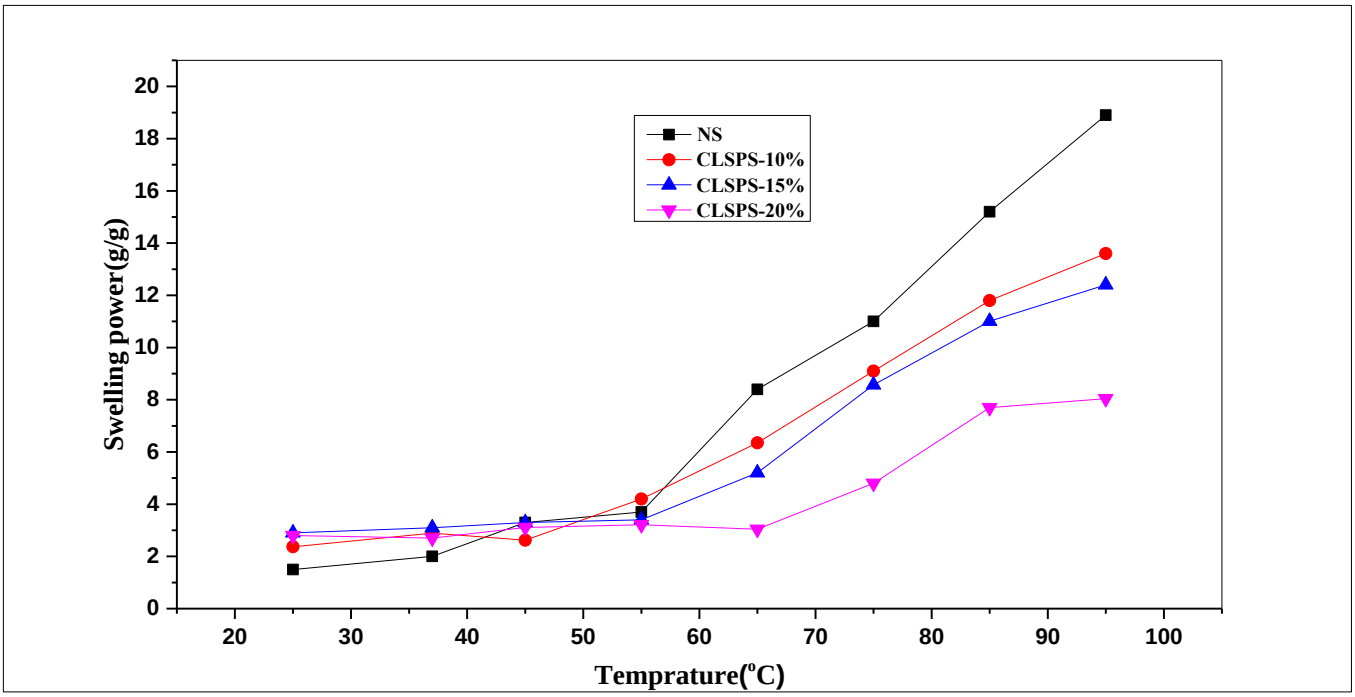


Figure 7: Swelling power of native and CLSPS at different temperatures.

Furthermore, cross-linking prevented starch granules from fully swelling during gel formation, and that the level of SHMP influenced the intensity of changes in swelling power and solubility of starch (Chantaro, Pongsawatmanit and Nishinari, 2013). Therefore, high degree of cross-linking can effectively prevent starch granules from swelling and being gelatinized. This information is important for industries that rely on starch-based products, as it can help them control the properties and behavior of their materials.

4.2.4 Moisture Content

The moisture content of the CLSPS powder was determined by comparing the weights of the powder before and after drying. As shown in Table 6, the moisture contents of the powder ranged from 14.55%±0.35 to 6.08% ± 0.404. the moisture content of native and CLSPS decreased in the following order: NS > 10%-CLSPS > 15%-CLSPS > 20%-CLSPS the values were 14.55± 0.35, 9± 1.08 7.166± 0.62 and 6.0834± 0.404 respectively. It was clear that cross-linking significantly reduces ($P < 0.05$) the moisture content of the NS. These finding was in close agreement with the data reported by Tesfay *et al.,* (2020). 20%-CLSPS with greater DCL exhibited a smaller weight difference and hence a lower moisture content when compared to starch with low DCL. The lower moisture content of CLSPS might be related to the cross-linking process, which stiffened and compressed the starch structure, limiting the ability of the starch granules to store water (Onofre, Wang and Mauromoustakos, 2009).

Table 6: Moisture content of both native and cross-linked sweet potato starch

Sample	NS	10%-CLSPS	15%-CLSPS	10%-CLPS
Moisture content (%)	14.55± 0.35	9± 1.08	7.166± 0.623	6.0834± 0.404

4.2.5 Moisture sorption pattern

Moisture has been identified as a factor that can change the flow and mechanical properties of several powders, including starches. Many types of dry powders that flow freely have a tendency to absorb moisture when they are transported or stored in conditions with inadequate temperature and humidity control. This can result in the formation of lumps, also known as caking (Jung, Lee and Yoon, 2018). The unfavorable effect of excessive moisture content on the flow of granules and powders may result in significant weight fluctuations during the packaging of granules into sachets, tablets, and capsules, especially when automated production techniques are used. In addition, operations such as mixing and transfer, as well as the stability of moisture-sensitive chemicals, might be undermined (Builders and

Arhewoh, 2016). As a result, when regulated powder flow or compaction is crucial, an understanding of the moisture sorption profiles of starches is required. When creating formulations, the hygroscopic nature of excipients and active substances should be considered. Higher water levels can cause microbial decomposition and a decline in starch quality (Gebre-Mariam and Schmidt, 1996).

Based on the current findings, it was observed that the powder samples, including both sweet potato starch and CLSPS, exhibited a more rapid uptake of moisture with increasing relative humidity (RH) level, as illustrated in figure 8, across different moisture levels, Notably, the CLSPSs showed comparatively lower water uptake across the entire range of relative humidity levels than their native counterparts, this suggests that as cross-linking increases, the moisture sorption of the starch reduced. These findings are consistent with a study reported by (Gao *et al.*, 2014), which observed that the use of sodium Tri metaphosphate (as a cross-linker) can enhance the intensity of ester-linkages (cross-linking bonds), thereby improving the stability and integrity of the starch granule structure. Moreover, Kulicke *et al*., (1990), reported that with an increase in the concentration of sodium Tri metaphosphate, the water sorption capacity of starch decreased due to the formation of diester phosphate linkage and a consequent reduction in mesh width and water absorption.

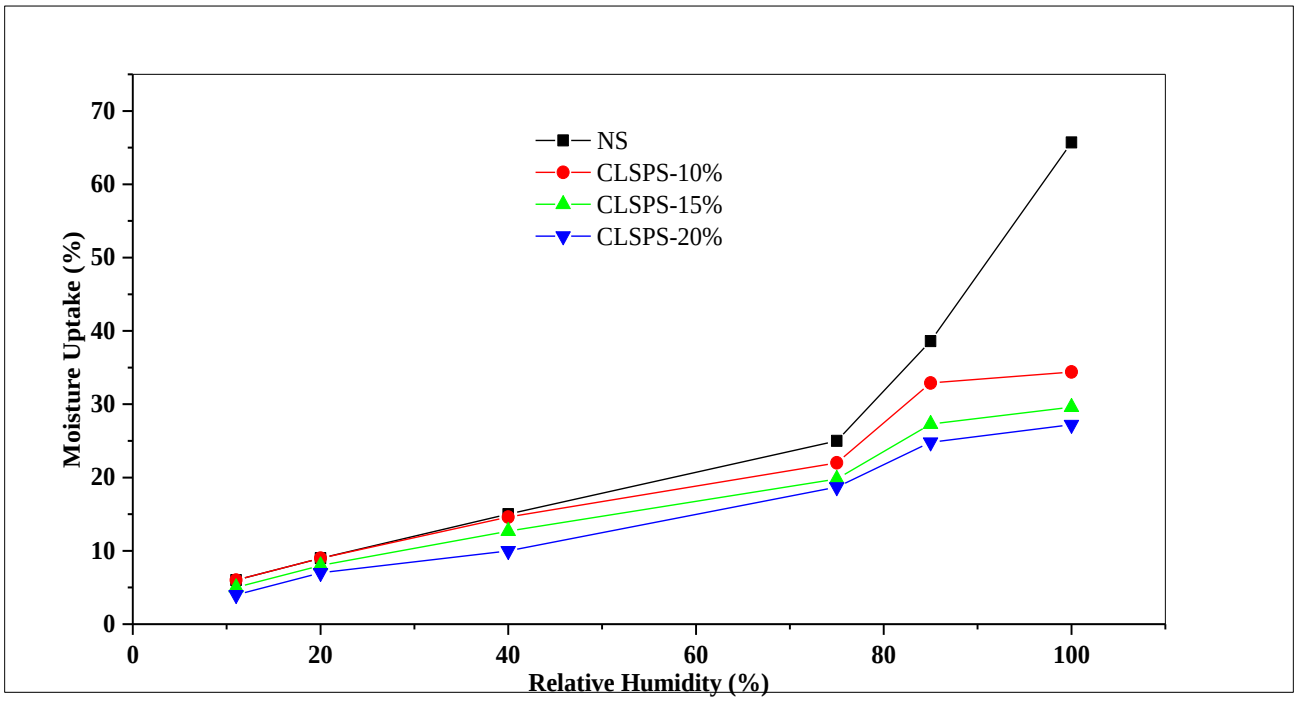


Figure 8: Moisture sorption patterns of native and CLSPSs after storage for 4 weeks.

4.2.6 Drug–Starch compatibility study

4.2.6.1 *Fourier Transformed- Infrared Spectroscopy (FT-IR) Analysis*

The purpose of drug-excipient compatibility studies is to identify, characterize, and predict possible interactions, as well as the influence of these interactions on the final drug product's manufacturability, quality, and performance (Dave *et al.*, 2015). FT-IR spectra of 20%-CLSPS, glibenclamide (GLB), and physical mixture (PM) are shown in figure. 9. The decision was made to select 20%-CLSPS for the FT-IR studies. Respective spectra were taken in the following regions: under 800 cm^{-1}, 500 cm^{-1} (the unique finger impression), somewhere in the range of 2,800 and 3,000 cm^{-1} (the C-H stretch area), lastly somewhere in the range of 3,000 and 3,600 cm^{-1} (O-H stretch area) (Surendra*et al.*, 2015).

The FT-IR spectrum of 20%-CLSPS presented two characteristic peaks at 2896 and 2988 cm^{-1} which are attributed to C–H bond stretching. The peak at 1407 cm^{-1} is ascribed to the bending modes of O–H and other characteristic peak were observed at 1076 cm^{-1}, 1407 cm^{-1} and 763 cm^{-1} for C–O, C=O stretching, and C–H of alkanes, respectively. This observation was nearly in agreement with a study done (Torrenegra *et al.*, 2018). The spectra of the GLB active agent showed two characteristic peaks at 3368 and 3315 cm^{-1} corresponding to the amide stretching bands, a C–H band at 2931 cm^{-1}, C=O stretching vibration at 1715 cm^{-1} and 1617 cm^{-1}, C=C stretching bands at 1521 and 1451 cm^{-1} and symmetric and asymmetric $S=O_2$ stretching at 1342 cm^{-1} and 1157 cm^{-1} respectively (Youssef *et al.*, 2021). The infrared (IR) spectra of the 1:1 ratio of the physical mixture (PM) of the drug with CLSPS-20 % showed characteristic amide peaks at 3368, 3315, and 1715 cm^{-1} carbonyl stretching (N-H stretching) vibration at 1617 and 1521cm^{-1}; and SO_2 stretching vibrations at 1157 and 1342 cm^{-1}.

The FT-IR spectra of PM containing glibenclamide exhibited specific peaks characteristic of the drug at the corresponding wavenumbers and similar peaks were also observed in the spectra of PM containing the excipient (20%-CLSPS), indicating that the chemical identity of glibenclamide was preserved in the mixture. However, in some cases, the intensity of the drug-related peaks was reduced or broadened in the presence of the excipient, which may be attributed to factors such as mixing or loss of crystallinity (Paixão *et al.*, 2021). Overall, the FT-IR data confirms that the excipient did not have any effects on the performance of the drug, indicating good compatibility between the two components.

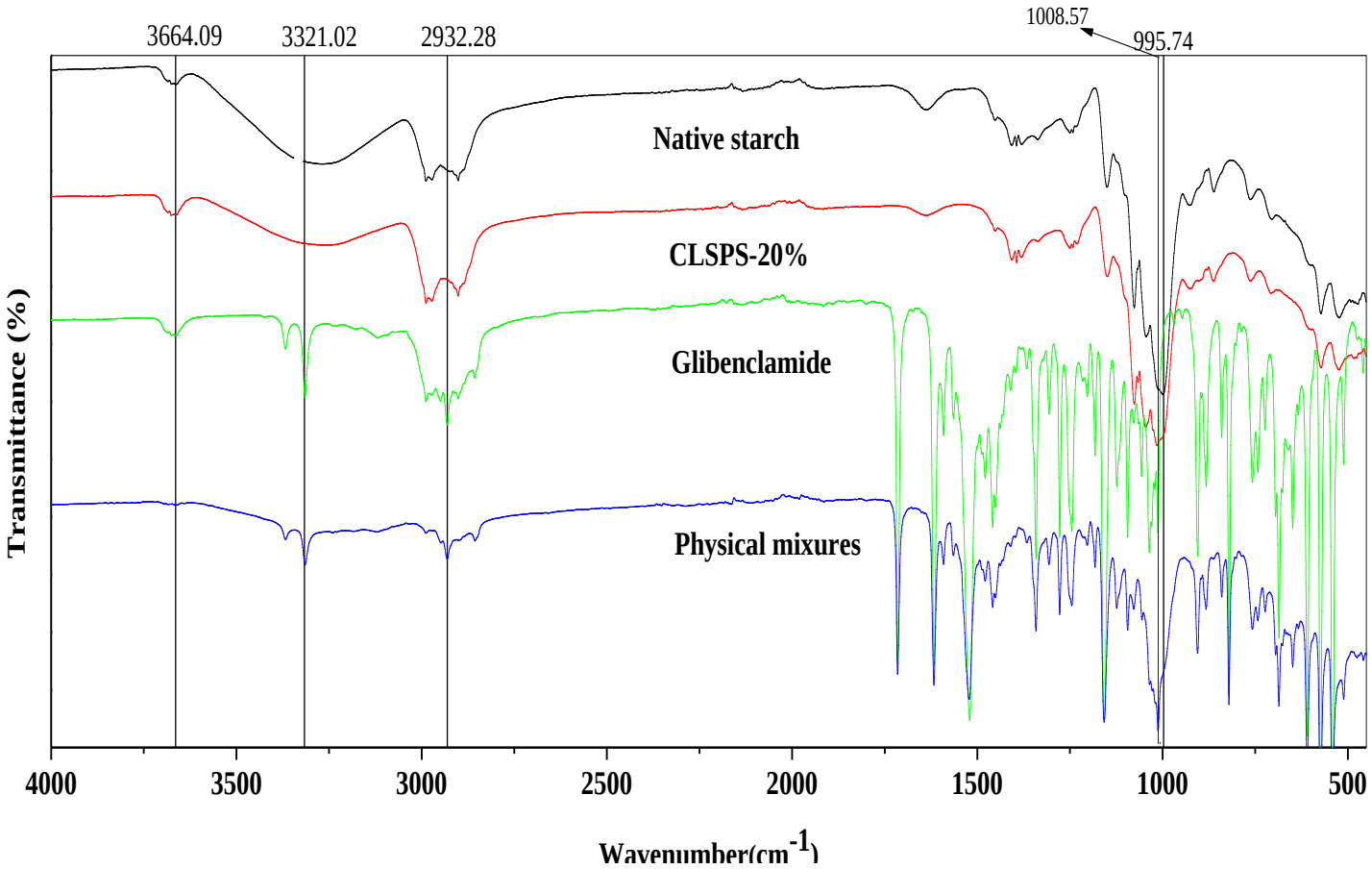


Figure 9: FT-IR spectra of NS, 20%-CLSPS, Glibenclamide and Physical mixture.

Table 7: Summery of IR interpretation of pure GLB drug along with its PM with 20%-CLSPS.

Functional groups	GLB pure drug	20%-CLSPS	PM of 20%-CLSPS-GLB
N-H stretching of CONH	3315 and 3368	---	3315 and 3368
C-H str CH3, CH_2 and OCH_3	2989,2931& 2856.	2988 and 2896	2989, 2931 and 2856.
C=O	1715	1641 (1650-1750)	1715
C=C ring stretching	1617 and 1522	_	1617 and 1522
C-H bending	1451 and 1342	1407 (1350-1500)	1459 and 1342
SO_2	1245 and 1278	-	1245 and 1278
C-O	1158	1150 (1000-1300)	1158
C-O-C	1065	1076 (1000-1300)	1078

4.2.6.2 *Differential scanning calorimeter (DSC) Studies*

The study of drug-excipient compatibility by DSC (SKZ1058B, CHINA,) is very important in the pharmaceutical industry**.** It reveals not only a variety of chemical interactions, but also physicochemical changes such as melting points, which may alter the effect of API. In general, DSC is a quick and reliable tool, and its thermogram has been used to investigate the thermal transformations that take place during heating in an inert atmosphere (Balen Saharia *et al*., 2021 and Dewan I. *et al*., 2015). It appears to be a good thermal analysis method for the thermo-mechanical properties of the proposed drug and polymer, allowing for the identification of any potential chemical interactions between the drug and the polymer backbone (Sachan, Ghosh and Bhattacharya, 2012).

Figure 10 shows a typical DSC curve for GLB, 20%-CLSPS, and PM at temperatures ranging from room temperature to 400 ^{O}C. The sharp endothermic peak of GLB was observed at 166.08ºC, corresponds to the drug melting point, which might be attributed to its crystalline nature (Siswanto *et al*., 2020). In the DSC thermogram of 20%-CLSPS, an exothermic peak was observed in the thermograms of the physical mixture (PM) of GLB-20%-CLSPS. The drug endothermic peak has very slightly shifted to a lower melting point in PM, which was recorded at 165.49^{0}C.

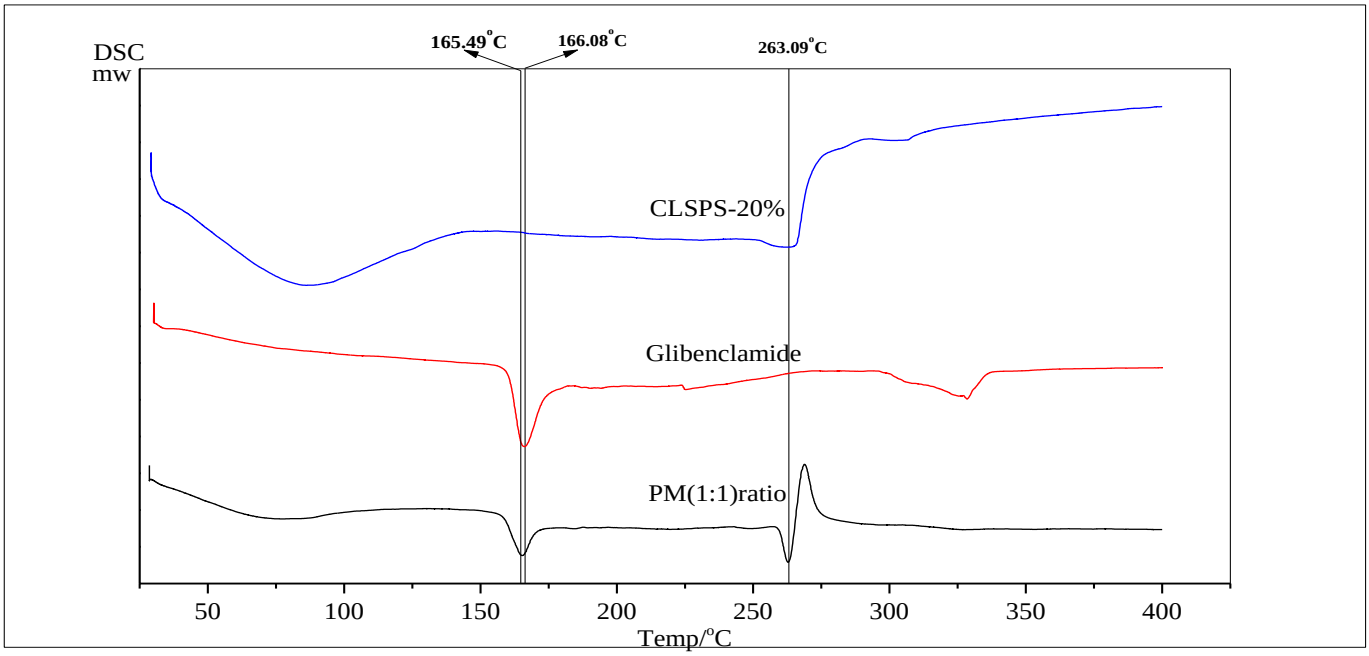


Figure 10: DSC thermogram of pure GLB, 20%-CLSPS, and their PM at (1:1 ratio)

The DSC thermogram of the physical mixture in this study also showed a GLB peak at 165.49^{0}C, this endothermic peak is almost close to 162-164 °C of Glibenclamide melting point. A comparison of these

two thermograms, i.e., GLB and its physical mixture, revealed an endothermic peak corresponding to the drug's melting point. Consequently, it was concluded that there was no indication of interaction between the GLB drug and the polymer (20%-CLSPS). Similar observations were also reported in previous studies by (Ahsan, *et al*., 2014), and (Hl and G, 2017), on GLB-tween-80 (GLB-T-80) study, and GLB-PVP polymer respectively. Despite slight differences in nature and appearance,

4.2.8 X-ray Diffractometry (XRD) analysis

4.2.8.1 Determination of crystallinity nature of starch

The presence and characteristics of the crystalline structure of the modified and native starch granules were investigated using XRD analysis. X-ray diffraction measurements were performed to check if chemical modifications altered the crystallinity of starch. In general, the starches were classified into A-C according to these patterns. Type C starch was made up of type A and type B crystallinities and could be further classified as C_A, C_C, and C_B based on the proportions of these crystallinities (Sci, *et al*., 2020). The ratio of starch crystallinity states (amorphous/crystalline) is critical for understanding its stability and application. The diffraction curve allows us to identify these characteristics as well as establish the starch classification (Cavalcanti, Farias and Cavalcante, 2019)**.**

The X-ray diffraction patterns of native, 15%-CLSPS, and 20%-CLSPS starch is shown in figure 11. Native starch gave strong diffraction peaks at 15.26°, 17.1°, and 22.97°, while 15%-CLSPS gave strong peaks at 15.33°, 17.22°, and 22.96°. In addition, 20%-CLSPS. exhibited strong diffraction peaks at 15.25°, 17.15° and 22.96°. Despite these slight variations, there was no significant difference observed between the crystallinity peaks of native and cross-linked starches. Both types of starch exhibited similar diffraction patterns with the typical characteristics of B-type starch. According to Agric *et al*., 2019, in general, the B-type diffraction pattern is common in tuber starches and has characteristic peaks at around 5.8, 15, 17, 23, and 24. The cross-linking alteration simply substitutes the starch functional group in the amylopectin and amylose chains, strengthening the starch granule without producing a new crystalline region (Amalia and Widiatningrum, 2021). These results indicated that cross-linking with SHMP up to 20% (w/w) did not dramatically alter the crystalline pattern of sweet potato starch.

The findings from various studies indicate that the cross-linking process has minimal impact on the X-ray pattern and crystalline structure of native starch. This is primarily because the phosphate cross-linking occurs predominantly within the amorphous portion of the starch granule, leaving the crystalline

pattern unaffected. Several studies, including those conducted by Sukhija, Singh and Riar, 2015, Chung *et al.*, 2007 and Błaszczak, 2020, Bruni *et al.*, 2018, and Kim and Lee, 2002.

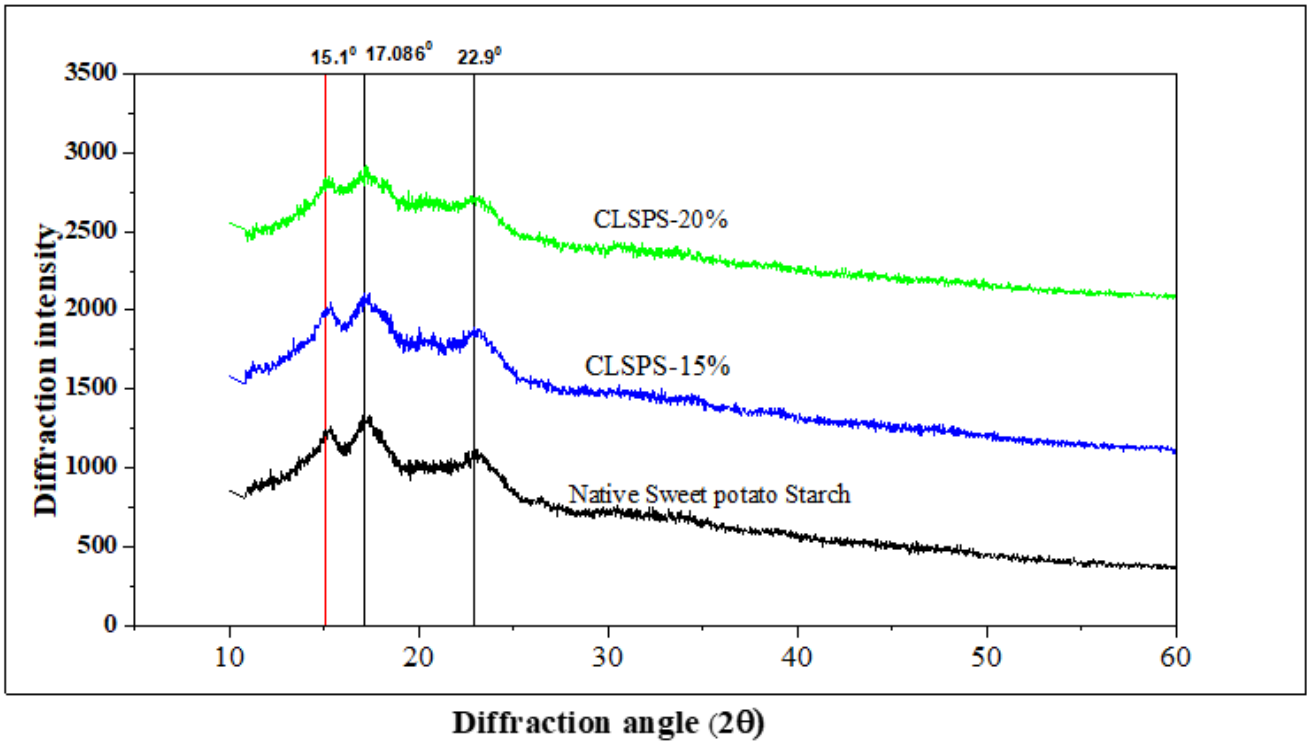


Figure 11: X-ray diffraction patterns of Native starch, 15%-CLSPS, and 20%-CLSPS

4.2.9 Studies of Thermal Properties

4.2.9.1 Thermogravimetry and Differential Thermal Analysis

The thermal analysis of TGA and DTA was used to evaluate the thermal behavior of uncross-linked as well as cross-linked starch. The experiments were carried out simultaneously at temperatures ranging from 30 to 800 ^{o}C, and the results for native, 15%-CLSPS, and 20%-CLSPS are presented in figures 12 and 13. The thermal degradation behavior of cross-linked starch exhibited noticeably different patterns with mass loss in steps as shown in the TGA curves from that of native starch. The crucial point in the TGA curves was determined to be the initial temperature of each component. Native and cross-linked starches degraded at four levels. The starch gradually loses weight during the first stage at temperatures between 100 and 275^{o}C due to the evaporation of water and other volatile compounds inside the starch, which determines how much mass is lost in this section. Current analysis observed that the small decline (-10.879 %, 12.38 % and 8.61 %) of the TGA analysis curve between 50–250 $^{\circ}$C for the native, 15%-CLSPS, and 20%-CLSPS, respectively. This indicated that small gas and moisture molecules were

released during this process, but the chemical structure of the sample remained unchanged. Thermal breakdown is typically considered to be the primary process involved in the degradation of starches. The significant weight loss observed during the second step of the experiment occurred at temperatures ranging from 295 to 437 ºC, 270 to 390 ºC, and 278 to 455 ºC for the native, 15%-CLSPS, and 20%-CLSPS samples, respectively. For native starches, the weight loss reached 69.445%, and it went down for modified starches to 63.64 and 59.66 %, which entered a thermal decomposition reaction. This weight loss can be attributed to the pyrolysis of starch and amylose; the third decomposition rate declined to 18.266%, 22.60%, and 15.32% after reaching the temperature (400-600ºC) and finally, the fourth step didn't show a significant change in the mass of the samples. Any weight loss beyond 600 ºC may be due to the decomposition of remaining carbonaceous materials (Christal *et al.*, no date).

The DTA curve shows up in figure 13. A slight peak was observed in all of the native and cross-linked starches and disappeared on the 20%-CLSPS curve at about 300 °C, which could be due to cross-link breakage during the early stage of decomposition. A more noticeable mass loss was also found, with maximal degradation rates peaking in the 15%-CLSPS and 20%-CLSPS on DTG curves at 402 and 463 °C, respectively. These temperatures, which fall between 290 and 600 °C, are appropriate for starch breakdown. The fact that the sharp peak has remained at a higher temperature in the case of 20%-CLSPS may be related to the high degree cross-linking, which gives the material greater thermal stability (Peixoto *et al.*, 2019). In all samples, as a result of the loss of water and volatiles, the mass loss started at about 100 °C. This was followed by the major degradation process, which began at 280 °C for the cross-linked starch (15% and 20%) and at 258 °C for the un-cross-linked one (NS). However, the consistency of mass degradation was not uniform across all steps. The first step of mass loss was lower for native starch than the 15%-CLSPS but much smaller for the 20%-CLSPS. Likewise, the second degradation step of modified starch had lower mass loss as compared to its native. In contrast, the third steps of mass loss for only 15%-CLSPS didn't show less mass loss than native starch, and the final steps didn't notice mass loss in all starch samples. Overall, the thermal stability of the CLSPS was relatively good.

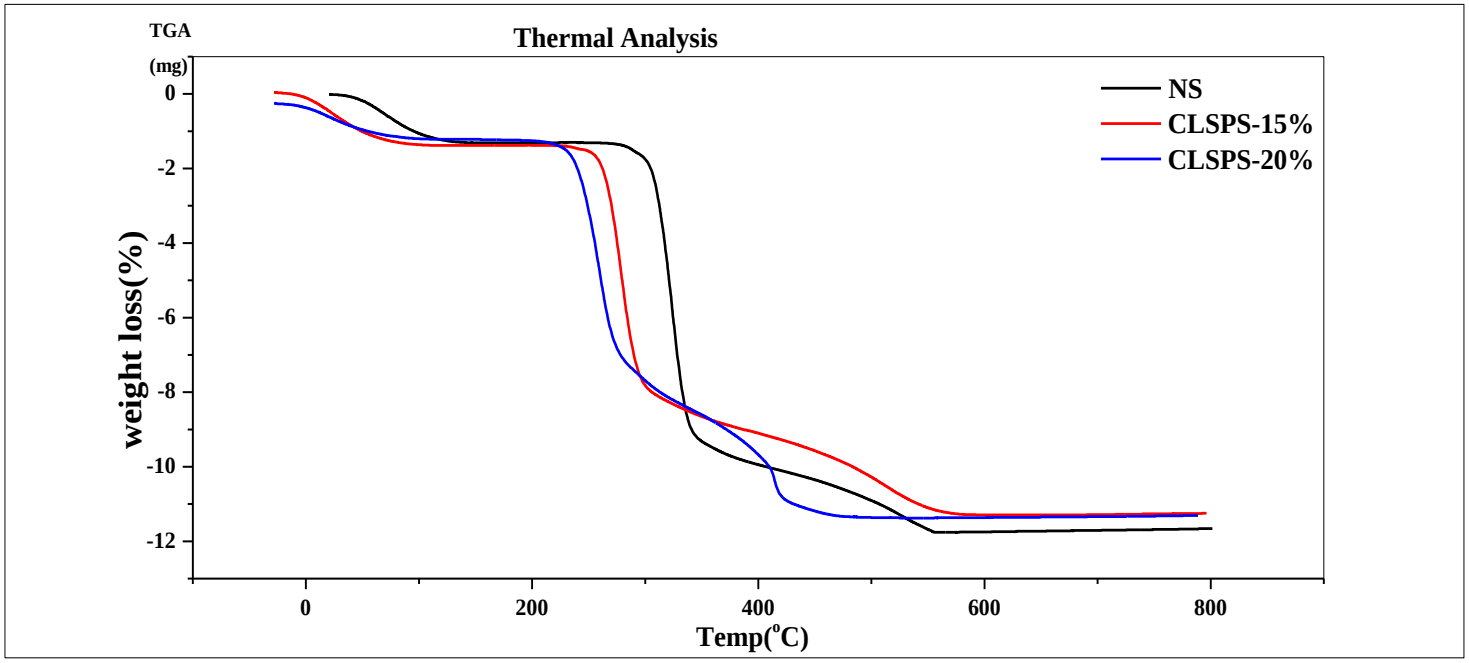


Figure 12: TGA curves for NS, 15%-CLSPS and 20%-CLSPS samples

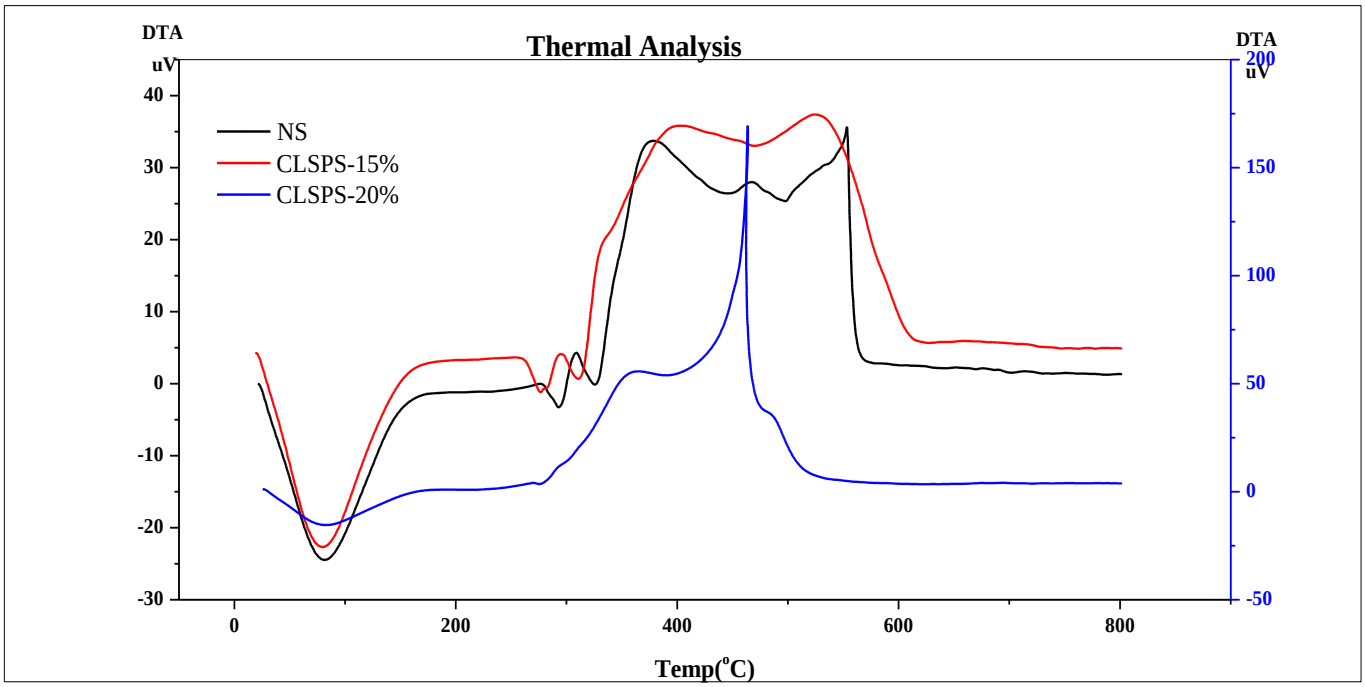


Figure 13: DTA curves for NS, 15%-CLSPS and 20%-CLSPS samples

4.2.10 Particle size and Surface morphology studies

4.2.10.1 Particle Size distribution

Particle size and size distribution analysis is crucial for understanding the flow behavior of a powder. This is because it enables the prediction of how the particles of the powder will pack and lock together, affecting its flowability and packing density (Psimadas *et al.*, 2012). However, presence of larger particles frequently improves a powder's flowability due to the increase in the interparticle void space and reduce the cohesive forces between particles, leading to improved flowability. This is commonly observed in the pharmaceutical industry (Wang, S., et al. 2019). This means that it may be challenging to forecast how a wider size distribution would affect the flowability of a powder (Stavrou *et al.*, 2020). The particle size distributions of native, 10%-CLSPS, &15%-CLSPS were shown in figure-14, on which all of them showed a monomodal normal particle size distribution with the average volumetric particle diameters being about 27.36, 37.04, and 44.37µm respectively. This indicated that the cross-linking increased the particle size of the starch granule. This finding corresponds well with previously reported by Li *et al.*, 2009 which stated that with increasing trisodium tri metaphosphate concentration from 0.1 to 0.4 g/g, the particle size of the starch granule increased, However, according to a study's contrarian report using epichlorohydrin as a cross-linking agent, the particle size generated as a microsphere decreased as cross-linking increased (Atyabi *et al.*, 2006).

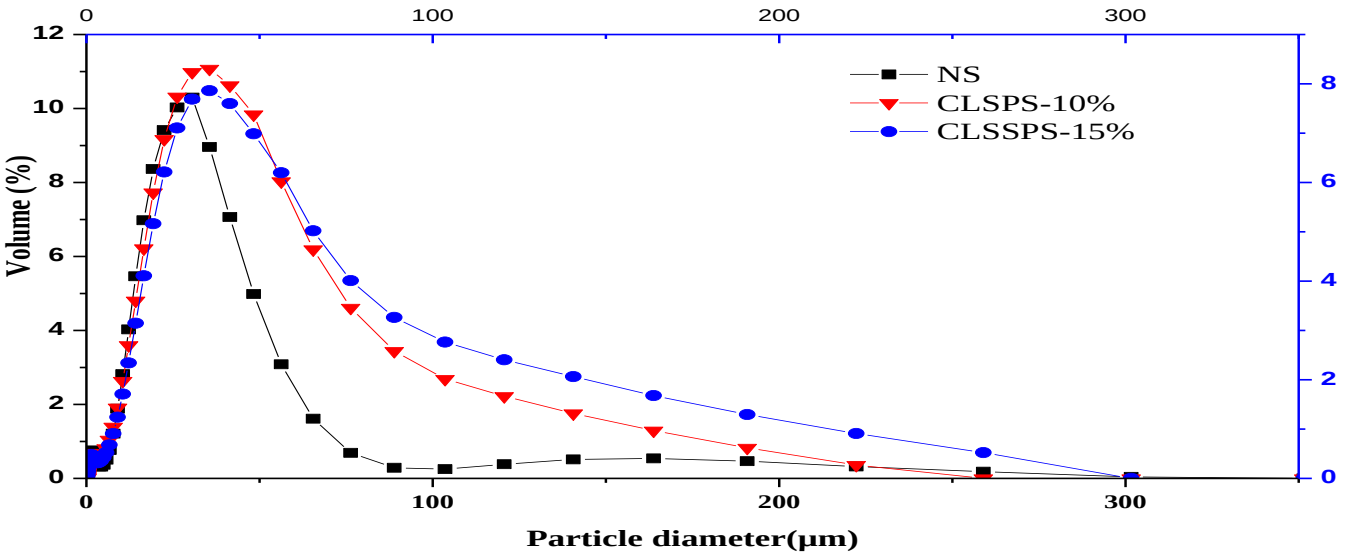


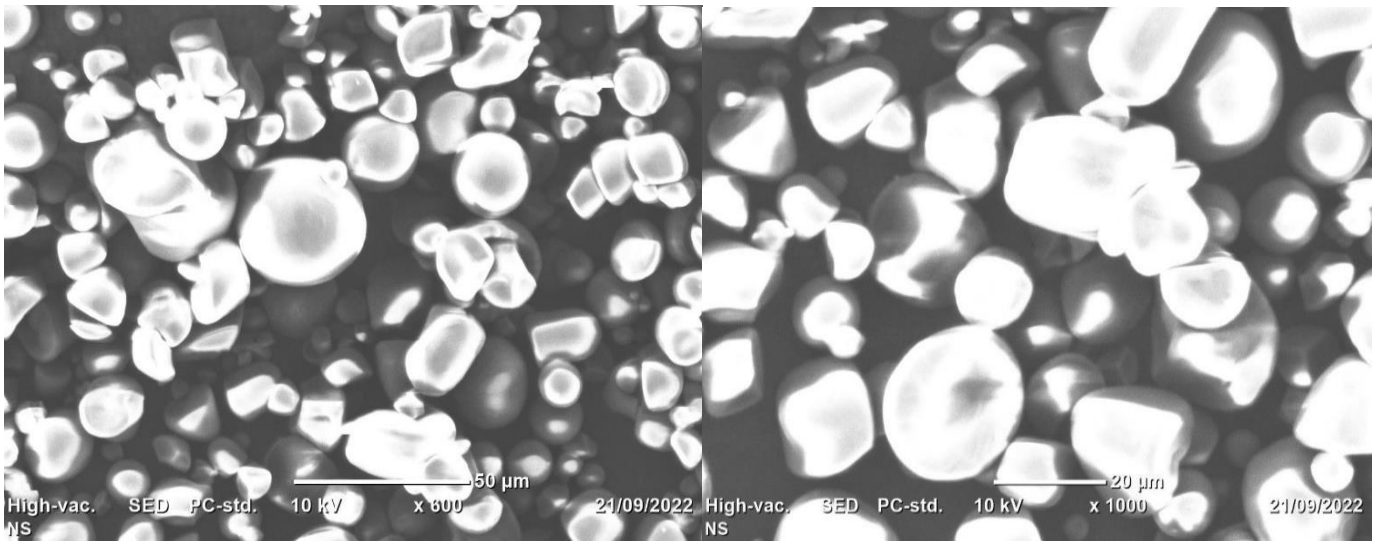
Figure 14: Volumetric granule size distribution of Native starch, 10%-CLSPS and 15%-CLSPS

Table 8: Particle size test on NS, 10%-CLSPS and 15%-CLSPS.

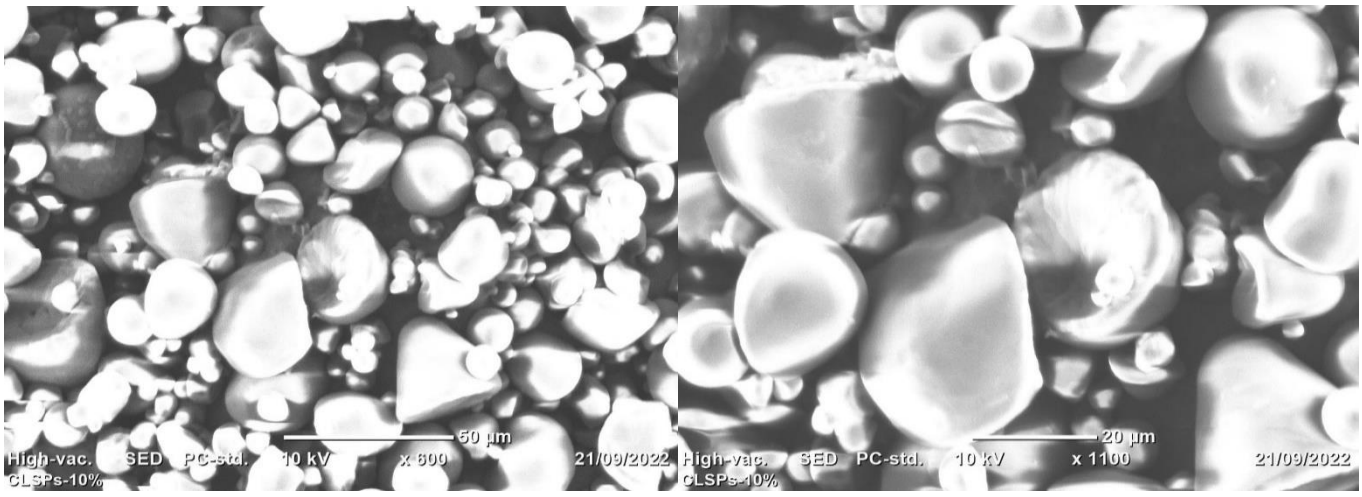
No.	Parameter of particle size	Type of starch		
		Native	10%-CLSPS	15%-CLSPS
1	Volume means diameter (µm)	27.36	37.04	44.37
2	Surface area mean diameter (µm)	7.40	8.21	8.87
3	10% of total particles	6.85	7.97	9.05
4	50% of total particles	21.26	29.01	32.09
5	90% of total particles	44.22	74.24	97.08
6	Specific surface area (m^2 /g)	0.6393	0. 5761	0.5337
7	Uniformity (deviation from median)	7.122E-01	7.276E-01	8.359E-01
8	Width of distribution (Span)	1.758E+00	2.284E+00	2.743E+00
9	Volume Concentration (%)	0.0156	0.0178	0.0229

4.2.10.2 Scanning Electron Microscope (SEM)

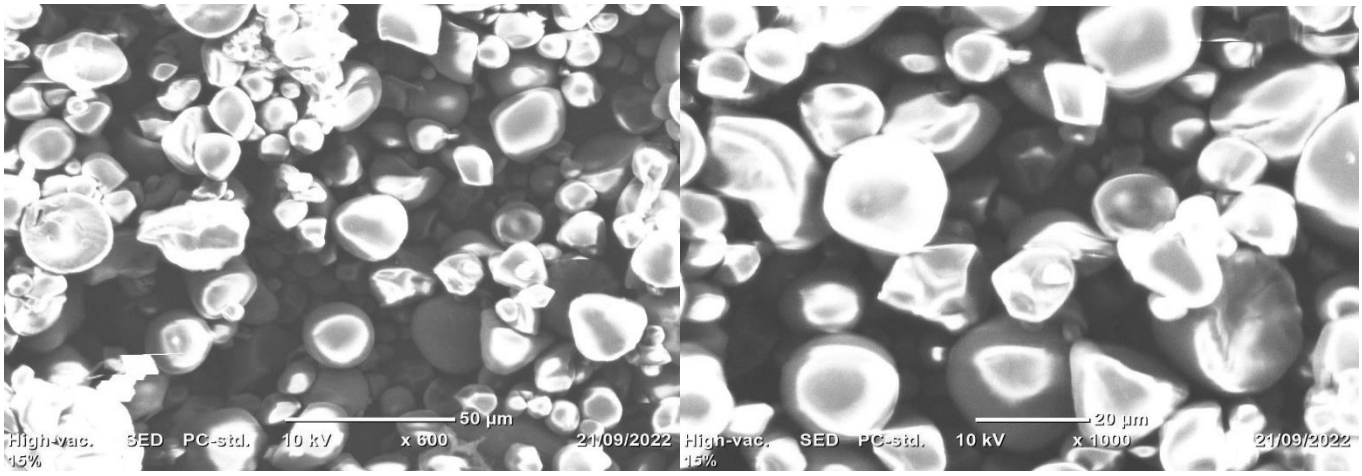
The scanning electron microscope (SEM) is one of the most capable tools available for investigating and interpreting surface morphology (Mahesh *et al*., 2020). SEM images of native, 10%-CLSPS and 15%-CLSPS are exhibited in figure 15. According to prior study by Zhang *et al*.., (2012), the native starch granules exhibit a range of shapes and sizes, including spherical and polygonal forms, with relatively smooth surface. According to scanning electron microscopy analysis, both the native and CLSPSs samples displayed starch granules of a similar shape, with no observable differences in their morphologies or external characteristics. This proved that the cross-linking levels used in the current study did not lead to any significant alteration in the physical appearance of the starch granules, which is comparable to what was reported by(Xiao *et al*., 2012), However, it should be noted that a separate study on microwave cross-linking of maize starch, conducted by (Gui-jie *et al*., 2006) demonstrated notable structural modifications in the starch granules. Furthermore, (Błaszczak, 2020) found that cross-linking starch with sodium trimetaphosphate did not impact its crystallinity, and the observed morphological changes on the surface of starch granules were primarily attributed to the alkali present in the suspension.



A) Native Starch



B) 10%-CLSPS



C) 15%-CLSPS

Figure 15: Micrographs of native and 10%-CLSPS, 15%-CLSPS with, 600x, 1000x magnitude.

4.2.11 Powder properties

The best solid dosage form manufacturer requires careful consideration of a number of variables, such as the powder properties that affect successful mixing process and the weight uniformity in compressed tablets. Efficient powder flow is crucial for achieving a uniform distribution of active substances and excipients in a tablet production process (Meng *et al*., 2016). It is also essential for robust tablet production and excellent compression equipment performance. However, variations in particle size and shape can make the process challenging, impacting packing arrangements and bulk/tapped density values. These variations can affect the tablet's weight, hardness, friability, and dissolution characteristics. Therefore, careful management of powder properties is crucial to ensure consistent product quality and performance (Kudo, Yasuda and Matsusaka, 2019).

The flow properties of modified starches (10%-CLSPS, 15%-CLSPS, and 20%-CLPS) were thoroughly analyzed and compared to native starch. Table 9 displays the results of the measurements included bulk density, tap density, flowability evaluated through Carr's index, Hausner's ratio, and angle of repose tests, with the value ranged from 14.026±0.535 to 11.77±0.9278 for Carr's index, 1.17±0.00736 to 1.13±0.0116 for Hausner's ratio, and 33.12°±0.636 to 29.99°±0.408 for angle of repose. These results provide insights into whether cross-linking improved the flowability and compressibility of the modified starches, as evidenced by their satisfactory flow properties. These properties are essential for the effectiveness and suitability of the starches for various applications. Furthermore, the results suggest that cross-linking influences particle compaction, where denser and stiffer powders require higher compression pressure to enhance their mechanical strength and cohesive impact (Femi-Oyewo, Ajala and Babs-Awolowo, 2015). Therefore, it is crucial to carefully control the cross-linking process during the production of CLSPSs to optimize their flow and compressibility properties.

Table 9: Powder properties of the native and CLSPSs (Mean ± SD, N= 3).

Parameters	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})
NS	0.5438 ±0.0061	0.6429±0.00854	15.40±2.045	1.18±0.028	©
10%-CLSPS	0.5998±0.0093	0.6976 ±0.0066	14.026±0.535	1.17±0.00736	33.12 ±0.636
15%-CLSPS	0.6384±0.0.0055	0.7408 ±0.00747	13.83±0.8123	1.16±0.010	32.054±0.116
20%-CLSPS	0.6845+0.0098	0.7758 ±0.0047	11.77±0.9278	1.13+0.0116	29.99 ±0.408

Parenthesis represent + SD, standard deviation, n=3 and © Powder didn't flow through the funnel.

4.3 Evaluation of tablets

4.3.1 Thickness

Tablet thickness is an important quality control test for tablet packaging. A thick tablet affect packaging, whether it is in a blister or a plastic container (Nahar *et al*., 2008). It is also an important consideration in packing operations and tablet counting with filling equipment that counts tablets based on uniform thickness. It is determined by the die of the tableting machine and is generally controlled to minimize appearance issues, ensure that tablets fit into the container, and that the filling equipment can count them accurately (Shah, B.A *et al*., 2018)

From the formulations uniform thickness of the tablets was observed, their mean thickness ranged from 4.24 to 4.89 mm. The average thicknesses of the tablets in all formulations were within the specified limits, according to the results shown in Table 10. This result is in close agreement with the study reported somewhere else by (Sürekli *et al.*, 2018). In general, tablet thickness is typically kept within 5% of the average value. It may be impossible to control unless raw material physical properties are closely controlled and upper and lower punch lengths are precisely and continuously standardized (Nahar, 2012).

4.3.2 Crushing strength

Hardness is also known as tablet crushing strength, which has been described as the force necessary to break a tablet in a diametral compression test. Hardness tests are employed to check if a tablet is strong enough to endure consumer handling, and to anticipate its durability against abrasion, breakage, and mechanical stability during packaging, storage, and transportation (Ahad *et al.*, 2009 and Article, 2011). Additionally, it might have an impact on the friability and length of tablet disintegration, the release, dissolution, and subsequently affect the bioavailability of drugs (Markl and Zeitler, 2017). Tablets that are too soft will not be able to endure handling and shipping, while those that are too hard may disintegrate too slowly. Sustained-release tablets are an example of a type of tablet that is designed to disintegrate gradually and has a high level of hardness. It's vital to keep in mind that tablet hardness is an empirical attribute even though it's beneficial for both quality assurance and in-process control. The effect of covalent cross-linking on the mechanical characteristics of dry tablets revealed that CLSPS-20 % containing tablets achieved the maximum hardness as shown in the Table 10. The hardness of all batches was found to be between 28.7 N$\pm$5.12 and 64.5 N$\pm$5.48, with an average of 52.24. The percentage deviation in hardness was 5.17N. However, hardness values are not an absolute indicator of tablet strength, and friability is another measure that should be considered.

4.3.3 Friability

Friability (F) measures tablets strength and is an indicator of their ability to tolerate pressure or stress during handling, packing, transit, and future usage (Singh, Kaur and McCarthy, 2007). Determination of tablet friability is supplements for other physical strength measurements, such as tablet crushing strength. As the results tabulated in Table 10 showed, the percentage of friability for a batch of the tablets ranges from 0.44±0.036 to 0.95+0.021 respectively. The % friability in all formulation tablets that lose less than 1% of their weight is generally considered to be acceptable and mechanically stable. In the present study, the friability values for all batches of formulations were found to be not more than (NMT) 1% thus ensuring that the friability is within the acceptable ranges.

4.3.4 Tensile strength

Tensile strength is a property of compressed material, and it is a fundamental criterion that ensures property constancy even when the size of the tablet is modified (Jarosz and Parrot, 1982). It might reveal information about the bonding strength and brittleness of the materials. In contrast to crushing strength, it takes compact dimensions into account (Tye, Sun and Amidon, 2005). As shown in the Table 10, the tensile strength of the tablets of all batches ranged from 0.278$\pm$2.08 to 1.28$\pm$1.83 Kg/cm^2. The tensile strengths of tablets made with CLSPS were greater than those of tablets prepared with their native counterparts. This is due to the fact that the cross-linked starch molecules are interconnected, which could increase the molecular weight of the starch and also provide better intermolecular interactions between molecules, leading to better tensile strength. Additionally, it also creates more carbon chains that are more hydrophobic compared to the non-cross-linked starch (Kim and Lee, 2002). The effect of cross-linking agent concentration in modified starch indicates that increasing the plastic deformation during compression leads to the formation of more solid bonds in the tablet, resulting in increased tensile strength, tablet disintegration, and dissolution times.

4.3.5 Weight Uniformity

The variation test of compressed tablets reveals the accuracy and uniformity of the dosage. The weight variation of all formulated matrix tablets was assessed as per the USP standard. As shown in Table 10, the average weight of 20 tablets in each batch ranged from 192.37 $\pm$ 0.41 to 212.5 $\pm$ 0.23. According to USP 30/NF 25 (2007), the maximum percentage variation permitted for average weight of tablets ranged between 130 and 324mg is 7.5%. The average percentage variation for all tablet formulations

was determined to be within the required limits. Therefore, every formulation complied with the test for weight variation.

4.3.6 Content uniformity

Tablet uniformity is significant because it ensures that each tablet has the proper amount of active ingredients with little variance across tablets within a batch. The uniformity of the API content in the completed drug product is a crucial requirement for ensuring the consistency of the dosage supplied to the patient. The acceptance criterion for assessing content homogeneity is defined by the US Pharmacopeia and other compendia. This standard requires that the potency of each dose unit must fall within a certain range, and that no more than a certain number of dosage units may exceed a tighter range (Ram and Ajit, *et al*., 2012). The content uniformity of each formulation (F1–F9) varied from 80.90–110.4%, as shown in Table 10, suggesting that the glibenclamide active agent was distributed consistently in the formulation. In addition, the matrix formation procedure did not affect the uniform distribution of glibenclamide in the matrix tablet. The quantity of glibenclamide in a tablet composition was within the acceptable range, according to the British Pharmacopoeia. These results agree with studies reported by (Azmi, Desrini and Article, 2015).

4.3.7 Disintegration time

Tablets prepared by 20%-CLSPS had a longer disintegration time than tablets made by 10%-CLSPS. In general, disintegration is a physical process that represents the breakup of inter-particle connections formed during tablet compaction (Silva and Webster, 2018). These indicate that tablets prepared from high concentrations of cross-linked starch disintegrated slower than those made with lower cross-linked starch concentrations may be a result of a reduction in hydration capacity and the swelling process of the modified starch consequent to cross-linking. These also suggests that increasing cross-linking agent concentration, perhaps, increases the number of cross-links which in turn confer greater stability on the starch granule and mechanical strengths. This may be the reason for the observed increase in disintegration time in tablets due to increased hardness of the tablets.

When the amount of cross-linking agent is increased, more chemical bonds are formed, which can lead to a denser and more compact tablet structure. However, it's important to note that increasing the amount of cross-linking agent beyond a certain point can have negative effects on tablet properties, such as delayed disintegration.

Table 10: Evaluation of Thickness, Hardness, weight variation, Friability, Tensile strength, Disintegration time and drug content uniformity of Glibenclamide Sustained-Release Tablets.

Fc	Thickness (mm)±SD n=10	Hardness (N) ± SD n=10	Average Weight (mg)±SD n=20	Friability (%) ±SD n=20	Tensile strength (Kg/cm^2)	Disintegration time (min) n=6	Content uniformity n=10
F_0	4.24±0.002	28.7±5.12	192.37±0.41	2.10± 0.12	0.278±2.08	26	®
F_1	4.23(0.003)	31.7±1.24	198.48±0.15	0.445±0.05	0.651±0.42	78	96.80%
F_2	4.32±0.004	46.7 ±7.68	194.83+0.21	0.50+0.041	1.30 ±1.72	98	89.50%
F_3	4.32±0.007	53.8±3.79	200.8±0.13	0.95+0.021	1.071±1.27	104	91.21%
F_4	4.75±0.002	56.9±4.45	204.3±0.16	0.246+0.12	1.035±1.50	108	93.64%
F_5	4.39±0.010	56.7±4.42	211.09±0.12	0.75+0.123	1.11±1.48	114	109.1%
F_6	4.89±0.008	60.7±7.10	211.2±0.17	0.74+0.231	1.07±2.60	>120	98.80%
F_7	4.3±0.0050	62.2±7.80	212.5±0.23	0.73+0.051	1.24±2.89	>120	99.91%
F_8	4.39±0.006	61.1±4.70	197.34+0.15	0.505+0.07	1.21±1.57	>120	80.90%
F_9	4.34±0.001	64.5±5.48	208.04+0.19	0.84+0.057	1.28±1.83	>120	110.4%

F_C= Formulation code, n: Number of tablets, SD= Standard deviation. ®= Test has not been done yet.

4.4 Standard calibration curve

A standard calibration curve for Glibenclamide (GLB) was prepared in 0.1M HCl and phosphate buffer pH 7.4 solution, as shown in Figures 16 and 17. A working solution of 100 µg/ml was prepared by dissolving an accurately weighed quantity of 10 mg of GLB working standard dissolved in a 30 ml beaker containing 10 ml of methanol, which was then sonicated for 10 minutes. The solution was then transferred to 100 ml volumetric flasks and diluted with 0.1N HCl and phosphate buffer to make a working solution at P^H 1.2 and 7.4, respectively. Aliquots of 1,2,3.4, 5,6 and 7 ml were pipetted out separately into a 20 ml volumetric flask and made into volumes to get a concentration range of 5-35 µg/ml respectively. The absorbance was measured at λmax of 228 nm using a U.V spectrophotometer-1600 PC. The calibration curve was constructed by plotting absorbance (Y) against concentration (C) in micrograms per milliliter. The linearity with regression equations were obtained y = 0.0199x - 0.0526, R^2 = 0.9998 and y = 0.02x + 0.0506, R^2 = 0.9999 in 0.1 N HCl and phosphate buffer pH 7.4, respectively.

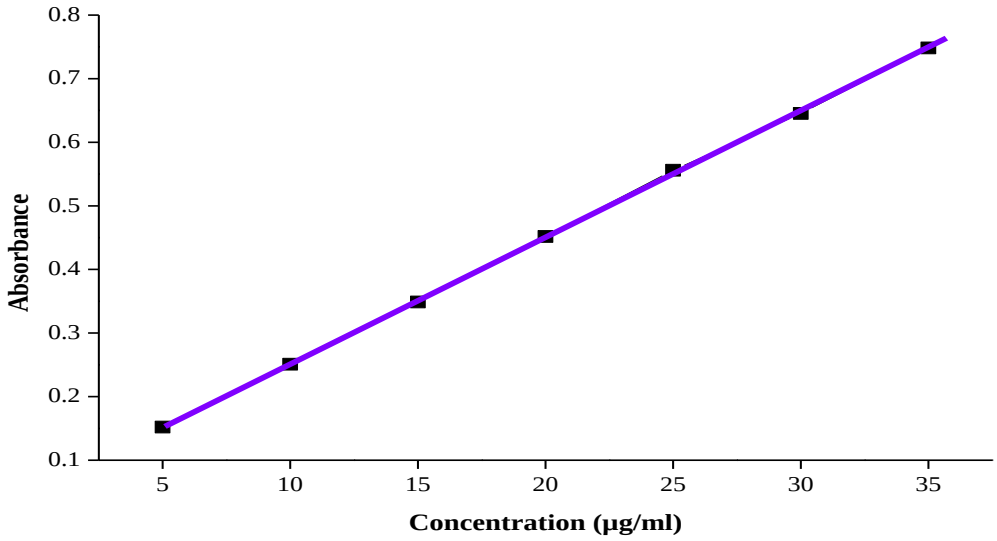


Figure 16: Glibenclamide standard calibration curve at λmax of 228 nm in 0.1N HCl (pH 1.2) with 95 % confidence interval for the triplicate mean.

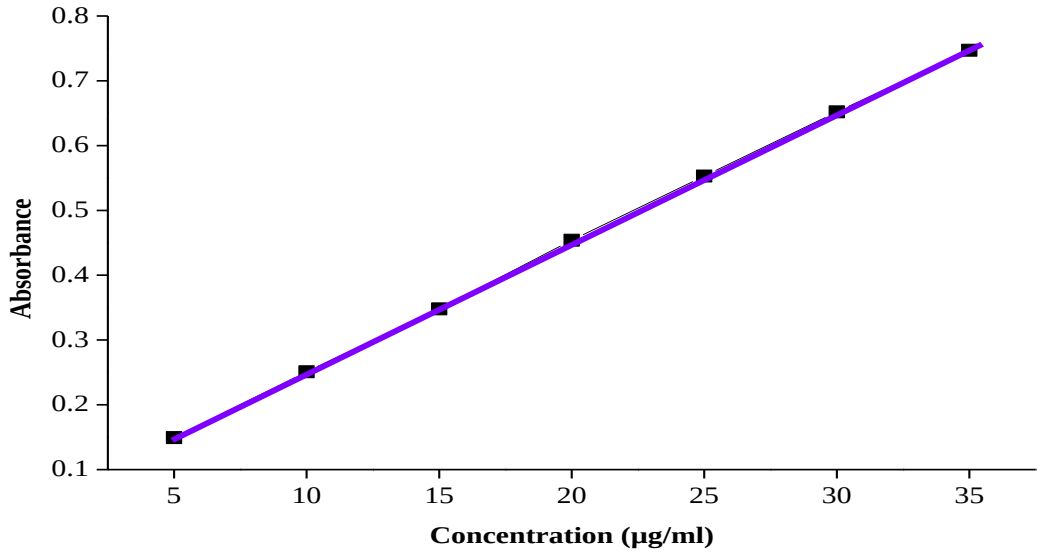


Figure 17: GLB standard calibration curve at λmax of 228 nm in phosphate buffer solution at pH 7.4 with 95 % confidence interval for the triplicate mean.

4.5 *In-vitro* dissolution studies for sustained release matrix tablet

In vitro dissolution/release tests are an important tool to ensure product quality and performance, and also assist in the product development and regulatory processes of drug delivery systems. Drug release from a matrix tablet is a mass transport phenomenon that typically comprises three phases. The initial process is liquid penetration into the dosage form, which is followed by drug dissolution and, eventually, drug diffusion (Efentakis and Peponaki, 2008). Moreover, when modified starch comes into contact with water, it creates a gel layer that controls how a drug dissolve. The process involves swelling, erosion of the matrix, and migration of the dissolved drug to the surrounding environment. The thickness of the gel layer, as well as diffusion through it and erosion of the layer, all contribute to the rate of dissolution control (Singh *et al*., 2007)

In the present study, the batch release patterns shown in Figure 18 illustrate that the level of cross-linking and concentration of matrix-forming polymers (CLSPS) have a significantly influence ($P < 0.05$) on the drug release rate. There was an inverse relationship observed between the CLSPS content in the formulation and the GLB release rate. The release profiles of GLB from matrix tablets were examined in two different buffer solutions to mimic the various physiological GI tracts. The medium of pH 1.2 was used for the first 2 hours, representing the gastric condition, and for the rest of the 10 hours in pH 7.4 buffer solution, which is simulated intestinal fluid was replaced. It was observed that the tablets formulated with a higher concentration of (20%-CLSPS) gave a lower percent drug release at all time points. From the release data, the total percentage of cross-linked starch polymers in the tablet was evaluated to determine drug release at three different concentrations: 50%, 60%, and 70% of 10%-CLSPS in the form of F_1, F_2, and F_3, respectively. The formulations F_1 and F_2 demonstrated early release of active agents, with over 89% of the drug released within 5 hours. In comparison, formulation F_3, which was made with 70 % of the same polymer, had 61.93% of DCL and released over 88% of the drug within 6 hours; whereas formulations F_4, F_5 and F_6, which were prepared with 15%-CLSPS as a matrix-forming polymer, had concentrations of 50%,60%, and 70% of the polymer, respectively. These polymers had a medium DCL (63.73%) and released approximately 85% of the drug within 8 hours since the matrix tablets disintegrated completely before that time. On the other hand, formulations F_7, F_8, and F_9 were prepared with 50%, 60%, and 70% of 20%-CLSPS, which had the greatest DCL (75.35%), exhibited better extended release, and released more than 81% of their content slowly over 12 hours.

The slower release of glibenclamide from formulations prepared with 20%-CLSPS polymer can be attributed to the presence of inter-chain ester linkages introduced into the polymer structure through the cross-linking reaction. This cross-linking likely produces a more rigid polymer structure, resulting in a more elastic and denser swollen matrix. This dense matrix would restrict the movement of polymer chains, thereby slowing down drug diffusion and release (Castro *et al.*, 2013). In other words, the cross-linked structure of 20%-CLSPS polymer probably forms a tighter matrix upon exposure to the release medium. This compact matrix structure would pose a greater barrier for drug diffusion, leading to a slower release of GLB as compared to the less cross-linked 10%-CLSPS &15% polymer. The higher degree of cross-linking in the 20%-CLSPS polymer is therefore responsible for its superior extended-release properties relative to the 15%-CLSPS polymer. Furthermore, the enhanced release retardant effect of the highest amount of CLSPSs could be attributed to the development of a thicker and more viscous gel barrier, which ultimately hindered the entry of the dissolution medium into the matrix and slowed down drug diffusion. It could also result from delayed matrix degradation and limiting the uptake of solvent molecules into the system (Wu, J., Zhang, *et al.*, 2020). It was evident that increasing the high cross-linked polymer content in the matrix increased the thickness of the gel barrier and ultimately inhibited drug release.

Therefore, the drug release studies showed that there was a clear relationship between the concentration of the cross-linked starch polymer and the rate of drug release. Specifically, it was found that as the concentration of CLSPS in the formulation increased, the rate of drug release decreased. This means that there is an inverse proportionality between the concentration of the CLSPS polymer and the rate of glibenclamide release.

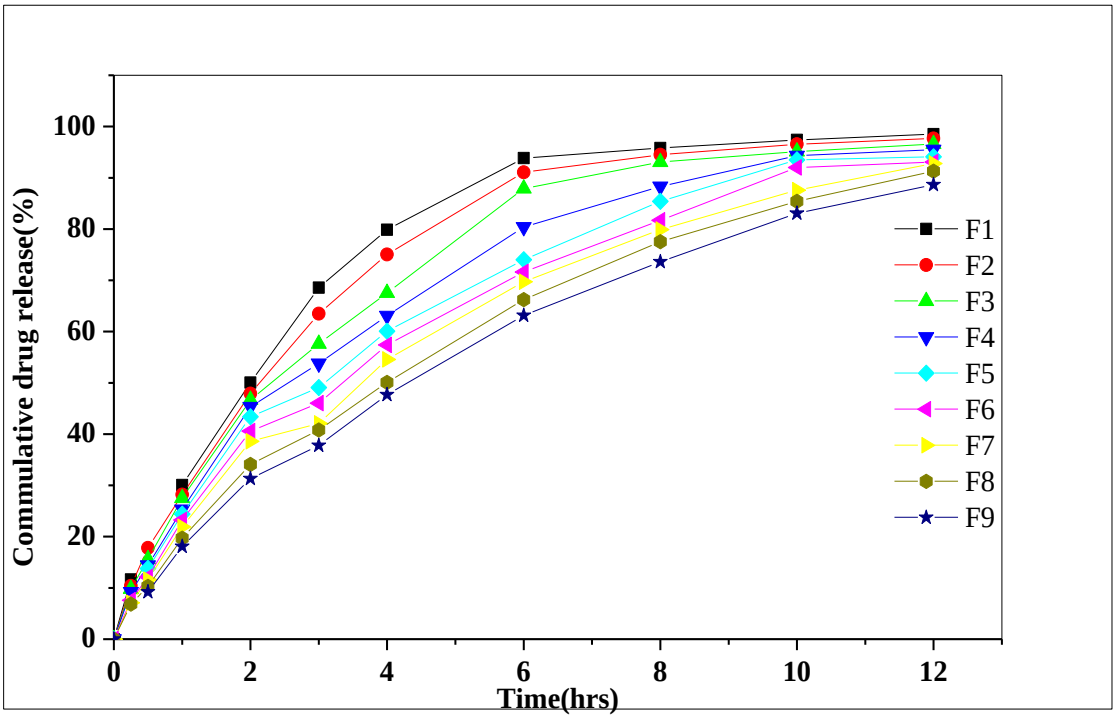


Figure 18: In vitro drug release profile of GLB sustained-release matrix tablets of all the prepared formulations in both 0.1N HCl and phosphate buffer solution of pH 7.4 at 37^{O}C. The results were presented as mean and standard deviation (n=3)

4.6 Drug release kinetics

In recent years, much study has been put into creating mathematical models that describe the drug release behavior of polymeric systems with controlled or sustained release. Studying dissolution kinetics has always been the primary factor used to evaluate a drug's performance. Several studies used both experimental data and theoretical models to describe drug release kinetics (Wu *et al.*, 2005). The release kinetics were evaluated by fitting the drug release data to five alternative kinetic models. Based on various mathematical models, the constant "k" represents the structural and geometric properties of a tablet, and the diffusional exponent "n" indicates the release mechanism, while the correlation coefficient "r" is employed to investigate the drug release pattern in a matrix system. In this current study, the most suitable release kinetics model was selected based on the highest r-squared value, as shown in Table 11.

Table 11: Mathematical modeling and drug release kinetics of the various formulations with their corresponding values of constant (k), release exponent (n) correlation coefficient (r^2) following linear regression of dissolution data.

Formulation code	Model								
	Zero Order		Higuchi		Hixson-Crowell		Kors Meyer Peppas		
	R^2	K_0 (μgh^{-1})	R^2	K_H($h^{-1/2}$)	R^2	K_{HC} ($h^{-1/3}$)	R^2	n	K_M(h^{-n})
F1	0.7022	7.2602	0.8883	34.52	0.7808	0.3047	0.9604	0.7367	0.5673
F2	0.8059	7.5508	0.934	32.40	0.7005	0.2653	0.9998	0.723	0.5988
F3	0.8464	7.5962	0.9573	32.20	0.7458	0.1887	0.9758	0.665	0.6141
F4	0.8802	7.5707	0.9753	31.766	0.7707	0.1923	0.9813	0.663	0.6269
F5	0.8862	7.7762	0.9783	32.6	0.7912	0.195	0.985	0.6303	0.6368
F6	0.9171	7.5448	0.9885	31.22	0.8011	0.2003	0.9858	0.6614	0.6637
F7	0.9394	7.4848	0.993	30.772	0.8176	0.2028	0.9886	0.6631	0.6738
F8	0.9448	7.4809	0.9955	30.551	0.8387	0.2978	0.9935	0.6857	0.6716
F9	0.9477	7.5333	0.997	30.79	0.8512	0.2112	0.9944	0.7049	0.7032

Notably, all formulations exhibited the highest r-squared values among the various drug release kinetic models studied. Further analysis revealed that the Higuchi model provided the best linear fit for the release profile, as evidenced by highest regression values and the plot of the fraction of GLB released against the square root of time. Therefore, the Higuchi model was considered the most appropriate for describing the drug release behavior in this study. It predicts that drug release is often simply a diffusion-controlled process via polymer matrix. From the release exponent in the Korsmeyer-Peppas model shows that the results of this investigation, with n values ranging from 0.6303 to 0.7367, indicate that non-Fickian (anomalous) transport mechanisms serve as the primary means by which drugs are released from starch matrix tablets (Luo *et al.*, 2009). It has also been attributed to structural reorganization, swelling, and disentanglement of polymer chains during degradation and release. Additionally, more than one process, namely erosion, swelling, and diffusion, is primarily used to regulate the release of the drug (Kannan, Manivannan and Ganesan, 2010). On top of that, the Korsmeyer-Peppas model predicts that drug release is most likely a diffusion and erosion-controlled process through the polymer matrix. Release from the biodegradable polymer matrix is typically regulated by the hydrolytic cleavage of polymer chains that causes matrix erosion, although diffusion may still be dominant when the erosion is slow (Yohanes, Yeng and Wang, 2006).

5. CONCLUSIONS

In conclusion, sweet potato starch was successfully modified through chemical cross-linking using sodium hexametaphosphate as the cross-linking agent. In general, cross-linked sweet potato starch has enhanced its rheological, physico-chemical, and thermal properties as compared to native starch. Specifically, the higher cross-linked starches exhibited lower peak viscosity but higher degree of cross-linking, indicating stronger intermolecular interactions and lower retrogradation tendency compared to the native starch. The cross-linked starches also showed reduced swelling power, solubility and moisture uptake. Moreover, they displayed improved flowability and compressibility relative to the native starch.

FTIR spectral and DSC analysis were instrumental in confirming that CLSPS were compatible with GLB. Moreover, the PXRD results indicated that cross-linking did not significantly influence the x-ray diffraction pattern of the native and cross-linked starches at any level of cross-linking. SEM image revealed no noticeable difference in granule shape and surface morphology between the native and cross-linked starches, and the thermal stability of cross-linked starch was exhibited relatively well as compared to unmodified starch.

It was determined that glibenclamide matrix tablets could be successfully prepared using a direct compression technique with various proportions of CLSPS. The cross-linking improved bonding observed during tableting due to increased compaction, which in effect resulted in higher crushing strength. The concentration and degree of cross-linking of polymers were found to have a significant effect on drug release rates, with higher concentrations leading to slower rates of drug release. Based on the above findings, it is possible to conclude that the new CLSPs starch-based polymer can be a potential candidate to be utilized as the sustained-release agents.

6. SUGGESTIONS

To further explore the potential of CLSPSs as a sustained-release pharmaceutical excipient, the following works are suggested.

- ✓ Conduct accelerated and long-term stability studies of CLSP starch.
- ✓ Investigate the *in-vivo* performance of CLSPSs in animal models and healthy human volunteers.

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Declaration

I declare that the thesis for the MSc Degree at Addis Ababa University, hereby submitted by me, is my original work and has not been submitted for a degree at this university or any other university, and that all reference materials contained therein have been duly acknowledged.

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