ADDIS ABABA UNIVERSITY
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CHARACTERIZATION AND EVALUATION OF LOCAL *STERCULIA SETIGERA* GUM AS A BINDER IN PARACETAMOL TABLET FORMULATIONS

BY;
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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 FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN PHARMACEUTICS

BY
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UNDER THE SUPERVISION OF DR. ANTENEH BELETE AND DR. GEBREMARIAM BIRHANU, DEPARTMENT OF PHARMACEUTICS AND SOCIAL PHARMACY, SCHOOL OF PHARMACY, COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY

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This is to certify that the thesis prepared by Chilot Abiyu, entitled **"Characterization and evaluation of local *Sterculia Setigera* gum as a binder in paracetamol tablet formulations"** submitted in partial fulfillment of the requirements of the Degree of Master of Science in Pharmaceutics complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Chair of Department

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ACRONYMS

ANOVA……..……. Analysis of Variance

API……. ….. Active Pharmaceutical Ingredient

BP……...…... British Pharmacopoeia

CFU……Colony Form Unit

CI…….……. Carr's Index

DBH…….…….... Diameter at Breast Height

DT……Disintegration Time

FTIR……...……...Fourier Transform Infrared Spectroscopy

GRAS……...……. Generally Recognized as Safe

HR……...Hausner Ratio

PVP…….…… Polyvinyl pyrrolidone

RH……... Relative Humidity

RPM…….…… Revolution per Minute

SD……...……. Standard Deviation

SP……. Swelling Power

TS……...……. Test Solution

UK……United Kingdom

USP/NF…….....United State Pharmacopoeia/National Formulary

USP……...United State Pharmacopeia

UV-Vis ……..……...……Ultraviolet – Visible Spectrophotometer

WSI…….……...Water Solubility Index

XRD…….…….....X-Ray Diffraction

ABSTRACT

Sterculia Setigera (*S. Setigera*) is a multipurpose wild plant in sub-Saharan Africa, primarily in Senegal and Ethiopia. It has many economical values. *Sterculia* Gum is an exudate product of *Sterculia* trees. It has a natural acid polysaccharide and produces galactose, rhamnose and galacturonic acid after hydrolysis. The aim of the present study is to characterize and evaluate the binding capacity of *S. setigera* gum in paracetamol tablet formulations.

The binding effect of the *Sterculia* gum was determined in different concentration (1%, 3%, 5%, and 7%). By using wet granulation method the granules were formulated with an average weight of 650 mg of Paracetamol made from *S. setigera* gum, Acacia, and polyvinyl pyrrolidone. The granules were compressed into tablets using a rotary tablet compression machine. The tablets were evaluated for its properties such as hardness, friability, disintegration and dissolution test. The binding nature of *Sterculia* gum was compared with the reference binders (Acacia and PVP).

The dry powder of *S. setigera* gum was obtained by solvent extraction, and its yielded 60% w/v. The Fourier transform infrared spectroscopic analysis showed that the formulation containing *S. setigera* gum was compatible with paracetamol in tablet formulations. The viscosity of *Sterculia* gum was higher than the reference binders. The tablet friability ranges from 1.4 to 0.44% and the disintegration time from 17 to 2 min. Tablets formulated with the *S. setigera* gum showed lower crushing strengths than those prepared with the reference binders. The drug release studies indicated that tablets prepared with PVP exhibited a higher release profile than Acacia and *S. setigera* gum binder. *Sterculia* gum is non-toxic, biodegradable and biocompatible excipient that can be employed as tablet binding agents.

Keywords: Gum, *Sterculia setigera*, Tablet binder, Paracetamol

1. INTRODUCTION

1.1 Gums

Gums are among the cheapest and most abundant raw materials that bigger plants commonly produced for protection purposes (Prajapati et al., 2013). The term "gum" was mainly applied to natural plant exudates that had oozed commonly from the barks of the tree and hardened upon exposure to air and sunlight (Nussinovitch, 2009). Natural gums are obtained as a by-product of the metabolic mechanisms of plants from natural sources and either absorbs water to form a viscous solution or are water-soluble (Kolhe et al., 2014).

Gums can be grouped mainly into three, namely, natural gums, modified gums, and synthetic gums. Natural gums exist in the natural state upon tapping or injuring the plant materials such as tree exudates or seaweed hydrocolloids. Natural gums are produced in response to tapping (known as exudate gums) or extracted from the internal part of seeds from legumes (known as extractive gums) (Barak et al., 2020). Gums are polysaccharides composed of several simple sugar units called monosaccharides tied by intermolecular glycosidic bonds. Gums can form complexes with calcium, magnesium, potassium and more complex substances such as polyuronides (Lujan-Medina et al., 2013).

Currently, plant-origin polymers are playing an important role in pharmaceutical applications such as binders, diluents, disintegrants in tablets, protective colloids in suspensions, thickeners in oral liquids, gelling agents in gels and bases in suppositories, and much lubrication during tablet manufacturing (Choudhary and Pawar, 2014).

1.2 *Sterculia setigera* plant

Sterculia setigera (S. setigera) is a multipurpose wild plant in sub-Saharan Africa, primarily known in Senegal and Ethiopia for its economic value. In this country, several studies about *S. setigera* were available on accessibility, socioeconomic impact, renewal, agroforestry, and sustainable gum collection. Because it is an exported product, the gum also contributes to increased income in rural areas (Atakpama et al., 2012). 95% of *S. sterculia* gum goes into the pharmaceutical industry and only 5% is used as a food preservative and stabilizer. The genus S. *sterculia* includes more than 300 species (Tadesse and Desalegn, 2009).

It belongs to the family *sterculiaceae*, which produces non-toxic safe gums for human consumption. *S. setigera* tree reaches up to 15-20 m at the top and 60 cm in diameter at the breast peak (Vollesen, 1995). *S. setigera* gum is the second essential gum next to Arabic gum. India and Senegal are important every day producers, overwhelmingly dominating the world market. The United States demands about 50% of the 4000-6000 tons of *S. setigera* gum collected globally, and Western Europe consumes around 30% (Tadesse and Desalegn, 2009). In Africa, Senegal is the largest producer of *S. setigera* gum. Sudan additionally exports small amounts, although it has the doable to produce and export a good deal more. *S. setigera* is commonly found in northern Ethiopia (Metema, Genda Wuha, Humera and some parts of Tigray region). Industrial purposes of *S. setigera* gum are comparable to Arabic gum. The plant and its exudates are shown in Figure 1 below.

a **b**

Figure 1: *Sterculia Setigera* tree (a) and Gum (b)

Sterculia gum is sometimes called Gum *karaya*. The dominant gum-producing species in different countries are: *S. urens* (India), *S. setigera* (Senegal and Ethiopia), S. *quinqueloba* (Malawi and Tanzania) (Tadesse and Desalegn, 2009). Plant polysaccharides (including gum and mucilage) are extensively investigated for use in developing different dosage forms since to comply as pharmaceutical excipients; it requires different properties, such as non-toxicity, stability, availability, and renewability. Various parts and products of *S. setigera* tree are used in traditional medicine to treat different diseases in Africa (Atakpama et al., 2012).

The stem bark is used to treat diarrhea, and the leaves to treat poison (Arrow) in Nigeria (Borokini and Omotayo, 2012). The bark and leaves of *S. setigera* are used as traditional remedies in Eritrea and Ethiopia. *S. setigera* gum is marketed at the local market mainly for therapeutic purposes in Eritrea (e.g., Barentu and Keren) (Lemenih and Kassa, 2011). It stabilizes salad dressings, cheese spreads and meat; prevents ice crystal growth in frozen foods; and improves the stability of whipped egg albumin and other protein foams (Pegg, 2012).

1.2.1 Collection of *Sterculia setigera* gum

More than 99% of *S. setigera* gum is collected from wild trees. The gum is gathered by means of natives who scar (tap) the tree with a knife, then return days later to harvest the tear of gum that has been fashioned on the scar. The gum starts off to exude at once, and the exudation continues for several days. Significant amount of exudation was taken place within the first 24 h. The gum is in the shape of large irregular tears. Acceptable high-quality gum is accumulated throughout April, May and June (Verbeken et al., 2003, Mujawamariya et al., 2014). During this time, as the weather gets hotter, the yield increases. On average 1-5 kg of gum was yield per tree and 4.3-7.2 kg during one year/season yield is sustainable production of gums without affecting trees (Tadesse and Desalegn, 2009).

Gums from different species exhibit traits that are intrinsically different. Even within the same species, distinctive types produce gums with different characteristics. Besides botanical sources, the season of collection, harvest, post-harvest therapy and other factors have an impact on the quality of the gum; these are the strategies of harvesting, cleaning, sorting and grading practices (Ahad et al., 2021). Tapping, for example gives more significant regular and high-quality gum than collection caused by using insect borers (World Health Organization, 2003). Better gum is obtained by collecting it on the tree rather than letting it fall on the ground. Above all, mixing the gum from different species at collection time or postharvest managing stage affects variability and the main reason for poor quality (Palada, 1996).

1.2.2 Physico-chemical properties of *Sterculia* gum

1.2.2.1 Chemical structure and composition

S. setigera gum is a complex rhamnogalacturonan-type partially acetylated polysaccharide (Vinod et al., 2010). It has a molecular weight of $16x10^3$ kDa, which is composed of 55-60% of impartial monosaccharide's (galactose and rhamnose), 8% of an acetyl group, and 37-40% of acid residues (galacouronic and glucuronic acids) (Lujan-Medina et al., 2013). The primary gum chain is shaped through α-D-galacuronic acid and L-rhamnose units. Side chains are linked to direct chain by 1, 2-β-D-galactose bonds or 1, 3-β-D-glucuronic bonds for galacturonic acid (Verbeken et al., 2003). It is commercially available as calcium and magnesium salt. The quality of the gum depends on the removal of impurities.

1.2.2.2 Physical properties of *Sterculia* gum

1.2.2.2.1 Solubility

The bodily residence of gum has significance in identifying its uses and industrial values. *S. setigera* gum is unique amongst the natural hydrocolloids due to its poorly soluble nature and its rapid and high water absorption characteristics, which swells to the shape of the viscous colloidal solution even at low concentrations (1% w/v) (Singh et al., 2008). The swelling reaction depends on the presence of acetyl groups in its structure. Deacetylation by using alkali treatment results in water-soluble gum. When used at higher concentrations in water (4%), *S. setigera* gum forms gels or pastes. Unlike other gums, *S. setigera* gum swells in 60% ethanol but remains insoluble in other organic solvents. *S. setigera* may take up to a hundred times its water weight (Casadei et al., 2010). Most frequent *S. setigera* gums can't be dissolved in water at high viscosities (Kulkarni Vishakha et al., 2012). Trivalent metallic salts will initiate the precipitation of *S. setigera* gum. The solution of *S. Setigera* gum is incompatible with soap-making emulsion (Mary, 2017).

1.2.2.2.2 Color and form

S. setigera gums, as looked at or collected in the normal state, are represented in a diversity of shapes and forms. They are available in spheroidal tears up to 32 mm in diameter, crystals,

granules, powder (by the mechanical process), spray and roller-dried powder (Arshi, 2011). The texture of most gums when fresh is perfectly smooth, but after some time it becomes rough or covered with minute cracks or striations due to weathering. The color of gums (in the solid state) varies from almost white through shades of yellow, amber and orange to dark brown. Color has great importance in the economic evaluation of *S. setigera* gums. Food-grade gum is usually a white to pinkish-gray powder with a slight vinegar odor from acetic acid release throughout storage (Sengkhamparn et al., 2009). Some of the best qualities of *S. setigera* gum are that almost colorless. On the other hand, dark, brownish-black or even black gums have sometimes occurred (Shekarforoush et al., 2016).

1.2.2.2.3 Rheological properties

S. setigera gum is the less water-soluble integrant of the gums group and produces solutions at small concentrations (<0.02% in cold water and 0.06% in hot water) (Verbeken et al., 2003). The viscosity of *S. setigera* gum in 0.5% dispersions has a value of 120-400 centipoises (cPs) (Sakib et al., 2019). Viscous solutions are obtained at increased concentrations and produce adequate molecular overlap. The native- and microwave-treated *S. setigera* exhibited a shear-thinning pseudo-plastic behavior in the aqueous system and oil-in-water emulsion (Shekarforoush et al., 2016).

1.2.2.2.4 pH stability

pH has an essential role in *S. setigera* gum dispersion stability, particularly at a pH range of 4.5-4.7. Viscosity diminishes when an acid or an alkali is added to the dispersion (Lujan-Medina et al., 2013). At pH above 8, *S. setigera* gum can undergo irreversible changes, due to loss of its acetyl groups. Because of the high level of uronic acid, *S. setigera* gum solutions are unaffected by acidic conditions, and they can resist the hydrolytic activity of 10% (w/v) HCl concentration. *S. setigera* gums are less soluble at most pH values but have maximum solubility at pH 6-8. Extraordinary viscosities and pH constancy are obtainable if gum hydration should be done before pH adjustment (Debon, 2001).

1.2.2.2.5 Heat stability

Dispersions of *S. setigera* gum are heat sensitive; upon heating, the polymer will change its conformation, ensuing in multiplied solubility and everlasting diminished viscosity. The dynamic oscillatory tests showed that the microwave-treated *S. setigera* gum had more gel-like behavior. When *S. setigera* gum was treated by microwave for 8–12 min, the viscosity of *Sterculia* was decreased by applying different heat and microwave treatments. The microwaved-treated gums showed lower viscosity than the native in the aqueous system and O/W emulsion (Shekarforoush et al., 2016). The significant effect of microwave treatment on the molecular structure *of S. setigera* gum might be explained. On the other hand, the microwave-treated but unheated gum brought higher viscosity than the microwave-treated and heated gum.

1.2.2.2.6 Moisture content and hardness

S. setigera gum varies in hardness. Hardness is governed partly by the amount of moisture present. According to united state pharmacopeia (USP), the limits are 15%. Materials containing less than 12% damage easily and produce dust during transportation and handling (Patel et al., 2011). Most gums break with clear glassy fracture when properly dried and may be readily pulverized to a form in which they are frequently used.

1.2.2.2.7 Ageing

Age of the *S. setigera* gum, i.e., the duration of time it has remained attached to the tree after secretion, may also affect some of its physical properties. The gum's color may also change from white to brown or dark-brown (Nussinovitch, 2009). The hardness can also change. Gum must be stored in dry places. Long storage decreases the viscosity of *S. setigera* gum because of loss of acetic acid. In powder form, gum viscosity decreases with age (Barak et al., 2020). Dilute *S. setigera* gum solutions of the same temperature and concentration have the same viscosity until the appearance of bacterial growth, which typically appears in two days after the solution, is prepared. The growth of bacteria reduces the stability of gum (Nieto, 2009).

1.2.2.2.8 Biological and toxicological properties

S. setigera gum is widely used in food and adhesive materials. It is non-toxic, tasteless, and does not affect the color, odor or flavor of the food or drug (Bahadur et al., 2017). It is classified as generally recognized as Safe (GRAS), which is listed under the Federal Food, Drug, and Cosmetic Act. It is generally approved that Sterculia gum has a low level of digestibility, and it will not contribute to calorie intake (Khan et al., 2011).

1.3 Pharmaceutical binders

Pharmaceutical binders are materials delivered in dry or liquid forms to prepare granules or to promote cohesive compacts in compressed tablets. Binders can be added to the powder as a dry powder or solution. Both dry binders and solution binders are involved in the granule preparation at comparatively minimum concentrations, typically at 2 - 10% by weight. These comprise of natural gums, alginic and alginates, starches, liquid glucose, cellulose derivatives and polyvinyl pyrrolidone (PVP) (Bhosale et al., 2014). The usual stability of economics and performance determines the business reality. Natural origin binders do have more advantages than artificial made binders, because naturally, they are non-toxic, much less costly and freely available. Natural gums can additionally be modified to have tailored substances for drug transport structures and as a result, can compete with the synthetic biodegradable excipients available in the market.

1.3.1 Acacia

Acacia is natural gum employed in solutions ranging from 10-25% concentration. These substances are extra high-quality when they are brought as solutions than when delivered dry to a direct compression formula (Ara et al., 2012). These herbal gums have the problem of being variable in their composition, and performances primarily based on their beginning and are heavily contaminated with bacteria. Therefore, their wet granulation mass is rapidly dried at a temperature above 37 ^{o}C to decrease bacteria proliferation.

1.3.2 Polyvinyl pyrrolidone

PVP is a synthetic polymer used as an adhesive in either an aqueous solution or alcohol. This versatility has expanded its popularity. Its concentration ranges from 0.5 - 5% solution (Kurakula et al., 2020).

1.4 Methods of incorporation of binders

Tablet uniformity is best achieved when the binding component is used in the solution as an adhesive. Binder in solution form is well distributed in the other chemical of the formulation and results in good interaction with minimum concentrations of binder. Besides that, powders vary with respect to the ease with which they can be wetted and their solubility time. It is desirable to incorporate binders in solution form. Some poorly compressible tablets like paracetamol, metronidazole, and acetazolamide can be effectively compressed when a liquid adhesive and moist granulation process is employed (Leucuta, 2012). The method of liquid addition can change from pouring the total amount of liquid at once to the pumping of liquid for a specific period in the course of granulation. Binder solutions are commonly made up of weight instead of volume.

1.5 Granulation

Granulation, a method of increasing the particle size by agglomeration mechanism is one of the most common techniques in the preparation of different pharmaceutical dosage forms, mainly orally taken dosage forms such as tablets and capsules. In granulation process, small or coarse particles are converted into large agglomerates called granules (Shaikh et al., 2018). Generally, granulation begins after the initial dry mixing of the excipients with the Active pharmaceutical ingredient (API); so that equal distribution of all substances at some level in the powder mixture is successful. However granules particle size used in the pharmaceutical company will be in the range of 0.2-0.5 mm to be either packed as a dosage form or mixed with different inactive ingredients before tablet compression (Parikh, 2016).

Granulation aims to increase the weight and content uniformity of active ingredients with excipients, to amplify the density of the blend so that it occupies less volume per unit weight for better storage and shipment, to facilitate flowability or volumetric dispensing, to limit dust all through granulation procedure to reduce toxic properties and process-related risk and to enhance the appearance of the product. Consequently, the ideal characteristics of granules encompass spherical form for freely flowing granules, the narrow particle size distribution for content uniformity and volumetric dispensing, small particle size to fill free space between granules for higher compaction, compression characteristics, and adequate moisture and hardness to prevent damage and dust formation upon prolonged storage.

1.5.2 Variables that affect granulation properties

Granulation is directly related to the compression and elegance of dosage forms. The quality of granulation is also affected by the materials used (formulation), processing techniques and equipment used. Among these factors, the materials used particularly binder employed are crucial for particle size uniformity, intergranular porosity, adequate hardness, compressibility and general quality of the granule. Binders are characterized by the different parameters, such as the mechanical properties of films, granules, tablets and the compressional properties of granules (Thapa et al., 2019).

1.5.3 Effect of binders on granule properties

Binding agent is one of the essential excipients in the granulation process. Most binding agents used for wet granulations, for example acacia are hydrophilic in nature (Kalasz, H., 2006). These binders increase the bulk density and decrease the porosity of granules, thereby reducing the effective surface area for evaporation. Hydrophilic binders can reduce moisture evaporation rate by decreasing the liquid vapor pressure. Besides more, the amount of water added into granules and retained by them after drying have highly affected with different binders. It has been also reported that the amount of moisture retained by granules after drying increased with the increasing concentration of the binding agents used (Mikolaitienė, 2017). Many studies have been done on the effect of different binders: acacia, gelatin, PVP, HPC, and methylcellulose solutions (Lang, 2018).

It was found that enhancing the binder concentration was directed by increases in the mean particle size, harder granules, reduces granule flowability and tapped density and hence reduces in granule porosity (Morkhade, 2017).

At high binder concentration the size of the particle similarly increased and associated with that the flow of the granule decreased. Investigations on the effects of using different grades of PVP in granules also showed that increasing the molecular mass of binder resulted in a decrease in granule friability (Cantor, 2008). The most significant variations in the physical properties affected by binder dilution were found in granule friability and bulk density. Precisely, the more dilute binder solution resulted in less friable granules. Also, significant influence was observed on inter particle porosity and thus on flow rate while insignificant effects was observed on average particle size and granule density. The mechanical properties of the granules and the corresponding compacts are mostly determined by the physicochemical interactions of the substrate-binder interfacial layer (Suresh, et al., 2017). The mechanical properties of granules and consequent compacts were correlated with the physicochemical characteristics (contact angle, surface tension and binder concentration) of the granulating liquid made of PVP (Cantor, 2008).

The mechanical properties of the single particles and compressed compact increased when the binder concentration in the granulation liquid increased until a certain limit above which the increasing granulation interaction angle reduce the binder distribution, making weak regions in the compact and decreasing its mechanical strength (Morkhade, 2017).

1.5.4 Effect of processing variables on granule properties

Granule characteristics are described to be influenced by equipment employed and processing variables such as the method of granulation, the volume of granulating fluid, massing time, and method of compressing the granules to tablets (Walker et.al. 2005).

There are many influencing factors on the processing variable (impeller speed, granulating solution addition rate, the amount of solution added in the granulation process, wet massing time, moisture content of the granulation after drying, and screen size used for the dry milling) in granulation characteristics using high shear mixer indicated that granulation growth (size) was improved by the increase in the amount of added water, high impeller speeds and short wet massing time (Badawy et. al., 2000).

Moisture content had the largest impact on granulation compressibility and tablet strength. Increasing wet massing time decreased granule porosity and fragmentation tendency hence increased granule strength, which led to granulation compressibility. It was reported granulation compressibility was extremely sensitive to processing conditions (Thapa et al., 2019).

Influence of drying temperature, drying process (tray- or freeze-drying), and granulation liquid viscosity on inter-and intra-granular drug migration was studied on both soluble and poorly soluble drugs. the inter and intra-granular drug distribution have not influenced by drying temperature, whereas uniform mixing of the drug in the granules intragranular migration was decreased as the granulation liquid viscosity increased (Abdul, et al. 2010). The physicochemical nature of the ingredients and binder solutions are the factors that affect the pharmaceutical granulations drying rate kinetics.

1.6 Granule flow

Glidant (talc) and lubricant (magnesium stearate) are added to promote the flow of the tablet granulation. These excipients often possess a coefficient of friction less than that of the bulk solid and hence improve the flowability thereby decreasing interparticle friction. Adequate mixing is needed for the homogenous distribution of lubricants and satisfactory granulation flow. The percent of fines, amount and type of granulating agent, particle size distribution, and type of glidant all have measurable effects on granule flow (Holm, 1997). Granules with a higher amount of fine indicate poor flow. A similar index has been defined by Hausner ratio by the equation: Hausner ratio = Tapped density/ bulk density.

Values less than 1.25 indicate good flow, while greater than 1.25 indicates poor flow (Wang et.al. 2010). Repose angle increases with increases in the percentage of fines. Values for angles of repose $< 30^{o}$ usually indicate a free-flowing material and angles $\geq 40^{o}$ suggest a poorly flowing material (Wang et.al. 2010). Flow rates are also a function of particle diameter. Tablet weight variation may be influenced by hopper flow rates if material flow to the feed frame is not consistent. Increasing formula weight (%w/w) of the binder was found to decrease the hopper flow rate. The decreased hopper flow rates are a result of the increase in average particle size that occurs as the formula weight of the binder was increased (Lakshman, 2011). However, at a constant formula weight of the binder, increasing the granulating liquid used to granulate resulted in granules that gave a higher hopper flow rate (Albaraki and Antony 2014).

1.7 Tablet compression

1.7.1 The process of compression

In tablet formulation, an appropriate volume of granules in a die cavity is compressed in between the upper and lower punch to produce solid tablet, which is sequential ejected from the die cavity as a tablet (Patel, 2006). The sequential events that occurred compression process with six steps are as follows, 1) transitional repacking, 2) deformation at points of contact, 3) fragmentation and/or deformation, 4) bonding, 5) deformation of the solid body, 6) decompression, and 7) ejection of the tablet. The process of compression is described in terms of the relative volume (ratio of the volume of the compressed mass to the volume of the mass at zero voids) and applied pressure (Kottke, 2002).

1.8 Significance of the study

The need for pharmaceuticals is growing with the increasing of human population and health problems which in turn increases the demand of pharmaceutical excipients. So, searching for alternative excipients to fulfill the demand is another area of solving the problem.

The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, and poor patient compliance. Apart from the impact on foreign currency, ordered chemicals typically are not delivered timely because of problems encountered in shipment, transportation and other related issues. Moreover, such study can be considered to satisfy the demands of the country for pharmaceutical and other sectors like food, textile, and paper industries.

The specific purpose of the present study was to characterize, and evaluate of *S. setigera* gum as binder in tablet formulations. Since, many of pharmaceutical companies in developing countries are mostly dependent on importing pharmaceutical raw materials. As a result, the finding of this study can contribute its part by evaluating the *S. setigera* gum as binding agent and based on the finding further scale up of the production. It also has potential applications as an alternative source of tablet binder.

Different researchers are investigating new excipients for potential use as binding agents in tablet formulations continuously, because of a need to achieve tablets with different mechanical

strengths and drug release properties for different pharmaceutical purposes. The pharmaceutical industries in developing countries import excipients and active ingredients despite the availability of local sources. But, producing and manufacturing excipients may not be as difficult as active ingredients which should be practiced locally, and in addition most of these imported excipients are almost synthetic polymers (Arnum, 2011).

2. OBJECTIVES OF THE STUDY

2.1. General Objective

To characterize and evaluate the binding capacity of *S. setigera* gum in paracetamol tablet formulations.

2.2. Specific Objectives

- To isolate and purify *S. setigera* gum from local source and characterize the physicochemical properties of *Sterculia* gum;
- To prepare granules by wet granulation method and characterize their physical properties (particle size, bulk density, tapped density, angle of repose, and flow rate);
- To evaluate the binding properties of *S. setigera* gum in paracetamol tablet formulations with natural (acacia) and synthetic (PVP) binders.

3. EXPERIMENTAL

3.1 Chemicals

S. setigera gum was obtained from the Natural Gum Processing and Marketing Enterprise of Ethiopia. Paracetamol powder BP (China Associate Co. Ltd, China) was donated by EPHARM, Iodine solution, ferric chloride, Distilled water, potassium phosphate monobasic (farmitalia caroerba, Italia), Hydrochloric acid, absolute ethanol (Carlo Erba Reagents, Italy), sodium hydroxide (BDH Laboratory Supplies, England), monobasic potassium diphosphate (ERBA Pharma Reagents Group, Italy), Lactose (BDH Chemicals Ltd., Poole England), PVP K-30 (China associate Co. Ltd, China), Acacia (BDH Chemicals Ltd., Poole, England), Talc (BDH Chemicals Ltd., Poole England), Corn starch and Magnesium stearate (BDH Chemicals Ltd., Poole England) were used as received.

3.2 Reagents

According to USP (USP 38/NF 33, 2015), Iodine test solution was prepared by adding 14 g of iodine into 36 g KI in 100 ml of distilled water in which 3 drops of HCl were added and then diluted to 1000 ml to detect the presence of starch.

Ferric chloride test solution was prepared by using 9 g of ferric chloride dissolved in water until 100 ml to identify the presence of tannins.

3.3 Methods

3.3.1 Isolation and purification of *S. setigera* gum

S. setigera gum obtained was dried in an oven (Kottermann® 2711, Germany) at 60 °C for 24 h. A 100g sample of the dried gum was ground in mortar and pestle into a fine powder and sieved in 224 µm sieve. The powdered gum was dissolved in distilled water and kept for 24 h with intermittent stirring at room temperature. The insoluble debris was removed by filtering in muslin cloth. Then, 90% ethanol was used to effect precipitation of the gum (1:4). The precipitated gum was separated from the hydro-alcoholic solution by filtering it through muslin cloth and was dried in an oven at 60 °C for 48 h.

The dried purified gum was powdered to fine particles and sieved through a 315 µm sieve, and stored in an airtight container. The percentage yield of the pure gum was determined using equation 3.1(Ameh, 2012).

$$\text{Percentage yield} = \frac{\text{Pure gum (g)}}{\text{Total sample gum (g)}} \text{x}100 \qquad (3.1)$$

3.3.2 Determination of physicochemical properties

3.3.2.1 **Organoleptic properties**

The purified gum was visually observed for physical characteristics such as organoleptic evaluations (colour, odour, shape, taste and special characters, such as touch and texture).

3.3.2.2 Presence of starch or dextrin

A 0.1 ml iodine TS was added to10 ml solution of the gum (10% w/v) to identify the presence of starch in *S. setigera* gum (BP, 2009).

3.3.2.3 Test for tannin bearing gums

A 0.1 ml Ferric chloride TS was prepared and then added to 10 ml of (10% w/v) of *S. setigera* gum solution to identify the presence of tannins (BP, 2009).

3.3.2.4 Determination of pH of gum

A 1% w/v solution of *S. setigera* gum was prepared in distilled water. The pH was then determined in triplicate using a calibrated pH meter (AD 8000, Japan) by triplicate measurements the mean value was taken (Hassan, 2010).

3.3.2.5 Melting point determination

The melting point of the gum was determined by capillary method. The fine powder of the gum was filled in capillary tube which is placed in melting point apparatus (Meka, et al., 2012). The temperature at which the powder melted completely was noticed.

3.3.2.6 Microbial Contamination

One gram of *S. setigera* gum powder was dissolved in 9 ml of distilled water. For detection of bacteria growth casein digest agar medium was used, and serially diluted to get 1:10 and 1:100. Viability of bacterial count was determined by using the pour plate method (Biswajit, et al., 2014). From each of the two dilutions, 1 ml was placed in a sterile petri dish and then, 20 ml of casein digest agar medium was added and allowed to solidify. The plates were incubated at 37 °C for 48 h. finally, the plates were checked for the growth and the total colony-forming units (CFU) were counted (Beuchat, et al., 1998)

$$\text{CFU/mL} = \frac{\text{CFU} * \text{dilution factor} * 1}{\text{aliquot}} \quad \text{.....(3.2)}$$

3.3.2.7 Loss on Drying:

Two grams of *Sterculia* gum powder was weighed and placed into a Petri dish and then dried in a hot air oven (Kottermann® 2711, Germany) at 105 °C for 2 h. The dried sample was cooled in a desiccator of dry atmosphere and then reweighed. The percentage loss of moisture on drying was calculated (Soni et al., 2019). Triplicate measurements were made and mean value was taken.

$$\text{LOD (\%)} = \frac{\text{Weight of water in sample}}{\text{Weight of dry sample}} \text{x100} \quad \text{.....(3.3)}$$

3.3.2.8 Relative solubility

The *Sterculia* gum solubility was determined in cold and hot distilled water, acetone, chloroform and ethanol employing the method described by (Kipo, et al., 2014). Accordingly, 1.0 g gum powder was dispersed in 10 ml of each of the above-mentioned solvents and left overnight. Then, 5 ml of the clear supernatants was taken in small pre-weighed evaporating dishes and heated to dryness for 2 h over a digital thermostatic water bath at 50 °C for the organic solvents and in a hot air oven at 105 °C for distilled water. The weights of the dried residues with reference to the volume of the solutions were determined using a digital analytic balance and expressed as the percentage solubility of the gum in the solvents. Triplicate measurements were made and average mean values were taken.

3.3.2.9 Ash Values

Ash values of the samples were determined based on the method described in the (B.P. 2009). A 2 g sample of powder was weighed in a pre-weighed ash crucible followed by heating in a furnace ((CARBOLITE, CWF 12/5, United Kingdom)) at 450 ^{o}C for 8 h. The sample was then removed and kept in a desiccator and weighed. Total ash values of the sample and water soluble ash were determined using Equation 3.4 and 3.5

$$Total\ ash\ (\%) = \left(\frac{m_1 - m_2}{m}\right) \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3.4)$$

Where, 'm_2' is mass of the ashing crucible, 'm_1' is mass of crucible plus ash and 'm' is mass of sample.

$$\text{Water soluble ash} = \text{weight of water soluble ash/weight of dried powder} \times 100 \ldots\ldots.(3.5)$$

3.3.2.10 Moisture sorption-desorption studies

A dried evaporating dish was weighed and 2 g of the gum powder was weighed into it. The final weight of the dish and powder was noted and it was placed over water in a desiccator for a period of 5 days. Thereafter, it was removed and transferred into another desiccator over activated silica gel (desiccant) for another 5 days (Desta, 2021).. The dish with its content was weighed on daily basis and its moisture content was calculated in triplicate.

3.3.2.11 Water solubility index and swelling power

Water solubility index and swelling power of the gum were determined according to the methods described (Desta, 2021). Initially, 0.5 g *Sterculia* gum powder was weighed directly into pre-weighed centrifuge tubes, and then 10 ml of distilled water was added to individual tubes. The tubes were then kept in a thermostatically controlled water bath at 25 ^{o}C for 30 min with frequent mixing at 2 min intervals. The tubes were then cooled centrifuged at 3000 rpm for 15 min. after the supernatant was removed, the sediment weight (Ws) was determined. The supernatant was dried to constant weight (W1) in an oven (Kottermann® 2711, Germany) at 60 ^{o}C for 12 hrs. The water solubility index (WSI) and swelling power (SP) of the gum were calculated using equations 3.6 and 3.7, respectively.

$$WSI = \frac{W1}{0.5} \text{ x } 100\% \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(3.6)$$

$$SP = \frac{\mathrm{Wsx100}}{0.5(100 - \mathrm{WSI})} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.7)$$

3.3.2.12 Viscosity of gum

Different concentrations (1, 3, 5 and 7%w/v) of S*terculia* gum, acacia, and PVP K-30 samples were prepared in a 100 ml beaker (Vilardell et al., 2016). Then, viscosity was measured using spindle number 3 of a Brookfield Viscometer (Engineering labs, INC, Middleboro, USA) at 100rpm. For each concentration, triplicate measurements were made and mean values were taken.

3.3.2.13 X-ray diffraction (XRD)

The X-ray powder diffraction patterns for the gum was scanned and recorded on a spectrometer equipped with anode X-ray generator from 10 - 40^{o} of 2- theta (scanning angle), using radiation generated at 30 mA and 40 kV(Ivanisevic et al., 2010).

3.3.2.14 Density and related properties of gum

Thirty grams of *S. setigera* gum was transferred into 250 ml measuring cylinder. The volume occupied by the gum powders was read and the bulk density was calculated as g/ml described under equation 3.8. The bulk in the cylinder was then tapped for 1 min using tapped densitometer (ERWEKA, SVM 20, Germany). This provided a fixed drop of one-half inch at rate 250 taps/min. The volume occupied by the gum was recorded and tapped density was calculated as g/ml. as described under equation 3.9. Based on the bulk and tapped densities, the Carr's index and Hausner ratio was calculated using Equation 3.10 and 3.11 respectively (Bashir and Haripriya, 2016).

$$Bulk\ density\ (\rho b) = \frac{mass\ of\ the\ powder}{bulk\ volume} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.8)$$

$$Tapped\ density\ (\rho t) = \frac{mass\ of\ the\ powder}{tappe\ volume} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.9)$$

$$\text{Carr's index (CI)} = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots (3.10)$$

$$\text{Hausner ratio (HR)} = \frac{tapped\ density}{bulk\ density} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3.11)$$

3.3.2.15 Flow rate and angle of repose

A standard glass funnel of 100 mm rim diameter, 60° bowl angle with a 91 mm stem length and a 7 mm internal stem diameter was fixed using a stand such that the bottom of the orifice is 10 cm above from the bench surface. The outlet was covered and the funnel was filled with 30 g of the gum powder. The content was then allowed to flow and the time taken for the powder to flow through the orifice was recorded (Meka, et al., 2012). The angle of repose and flow rate were calculated using equations 3.12 and 3.13, respectively. The values were the mean of three determinations.

$$\text{Angle of repose (AR)} = (\theta) = \tan(^{-1})\frac{h}{r} \quad \text{.....(3.12)}$$

Where h: height of pile and r is the radius of pile

$$Flow\ rate\ (g/sec) = \frac{\text{mass of powder}}{\text{time}} \quad \text{.....(3.13)}$$

3.3.2.16 Fourier Transform Infrared Spectroscopy (FTIR)

Sample of extracted *S. setigera* gum was analyzed in order to characterize its structure and to check drug excipient compatibility. The gum, pure paracetamol, and a mixture of gum and paracetamol (1:1) were mixed with FTIR grade KBr in the ratio 100:1 using paraffin as a film forming agent. The well-ground and mixed powdered samples were compressed into KBr disks by applying a pressure in a hydraulic press and were scanned over a wave number of 4000-400 cm^{-1} in an FTIR spectrometer (Shimadzu, FTIR-8400S, and Germany). Each FTIR spectrum was collected with 20 scans and spectral resolution 8 cm^{-1} (Tyagi et al., 2006). The major peaks of FTIR spectra of paracetamol in the mixture were analyzed and compared with the IR spectra of paracetamol alone.

3.4 Preparation and evaluation of granules

3.4.1 Wet granulation

The granules were prepared by wet granulation method. Paracetamol was used as a model drug to formulate the granules. Corn starch and Lactose was used as disintegrant and diluent,

respectively. The desired quantities of paracetamol and excipients were dry mixed for 5 min using a Turbula mixer (Willy A. Bachofen AG, Turbula Switzerland).

The mixture was moistened by gradual addition of exact amount of the wet granulating fluid containing various concentrations of binders. Wet massing was continued for 5 min. The wet mass was granulated by passing through a 1.6 µm sieve, dried for 24 h in oven. The dried granules were passed through a 1 µm sieve and then stored in air-tight containers and the same procedure was followed for Acacia and PVP formulations (see Table 1).

Table 1: Composition of the different batches of paracetamol tablets using *S. setigera* gum, PVP and acacia as binders.

Ingredients	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**
Paracetamol (API)(mg)	500	500	500	500	500	500	500	500	500	500	500	500
Sterculia gum (mg)	6.5	19.5	32.5	45.5	-	-	-	-	-	-	-	-
Acacia(mg)	-	-	-	-	6.5	19.5	32.5	45.5	-	-	-	-
PVP (mg)	-	-	-	-	-	-	-	-	6.5	19.5	32.5	45.5
Corn starch(mg)	65	65	65	65	65	65	65	65	65	65	65	65
Talc(mg)	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5
Magnesium stearate(mg)	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25
Lactose(mg)	68.75	55.75	42.75	29.75	68.75	55.75	42.75	29.75	68.75	55.75	42.75	29.75
Distilled water	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Total Weight(mg)	650	650	650	650	650	650	650	650	650	650	650	650

3.4.2 Characterization of granules

3.4.2.1 Moisture content

Moisture content of the granules was determined gravimetrically by taking 5 g from each batch of granules and heating the samples in an oven at 105 ^{o}C until constant mass was obtained. The granules were weighed immediately and the loss in weight was taken as moisture content of the granules.

3.4.3.2 Size distribution of granules

Thirty grams of each batch of granules were put in a set of sieves (ERWEKA, type, Germany) arranged in mesh size from top to bottom. Sieve analysis for particle size distribution of granules was performed using sieve shaker for 5 min. Each sieve along with the retained particles was weighed separately after well shake. The granules retained on each sieve were weighed and percent granules retained & mean granule size was calculated. The average granule size on any sieve was determined in microns as the mean size of the two successive sieves through which the granules passed and were retained (Shekunov, 2007).

3.4.2.3 Density and Related Properties of granules

Thirty grams of sample was poured in a 250 ml graduated cylinder. The cylinder was lightly tapped twice to collect all the powder from the wall of the cylinder. The volume was then read directly from the cylinder to calculate the bulk density according to the relationship: mass/ volume. The bulk in the cylinder was then tapped 500 times using tapped densitometer (ERWEKA, SVM 20, Germany) and the volume of the sample was recorded to calculate the tapped density. From the data of bulk density (ρ_0) and tapped density (ρ_t), Carr's index and Hausner ratio were calculated using equations in section 3.3.2.14 (Bashir and Haripriya, 2016).

3.4.2.4 Determination of granule flow rate and angle of repose

Thirty grams of each batch of granules were poured in a standard glass funnel of 100 mm rim diameter, 60^{o} bowl angle with a 91 mm stem length and a 7 mm internal stem diameter was fixed by using a stand such that the bottom of the orifice is adjusted that 10 cm above from the bench surface.

The content was allowed to pour out and the time taken for the granule to flow through the orifice was recorded. The angle of repose and flow rate were calculated using equation 3.11 and 3.12 described in section 3.3.2.15. The average mean value of three determinations was taken.

3.4.2.5 Determination of granule friability

Ten grams of each batch of the granules larger than 315 µm were put in a friability tester (ERWEKA type TAR-20, Germany), and allowed to revolve for 4 min at 25 rpm. The granules were then sieved using 315 µm sieves and friability was calculated by the equation described below. Percent friability recorded was average of three determinations.

$$\% \text{ friability} = \frac{(W1-W2)}{W1} X\ 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 3.14$$

W1 = initial Weight before test

W2 = final weight after test

3.5 Preparation and evaluation of tablets

The granules with average weight of 650mg made from *S. setigera* gum, Acacia and PVP were compressed into tablet using rotary tablet compression machine (Shanghai Chengxiag Machinery, Co., Ltd, China). The tablet compression force was adjusted by using lactose mono hydrate powder and its hardness was determined. The 16-mm die and flat-faced punches were used. Talc (1%) and Magnesium stearate (0.5%) were used to improve flow and to lubricate the die and punch surfaces before compression to avoid sticking, respectively. The prepared tablets were kept overnight in sealed bags before they were evaluated.

3.5.1 Weight and thickness of tablets

Twenty tablets were randomly selected from each batch and assessed gravimetrically on an individual basis using an analytical balance (Mettler Toledo, PR 203, and Switzerland). The average weight and standard deviation were calculated. For thickness, 10 tablets were randomly selected and each tablet was placed between the two arms of the Vernier Caliper (Nippon Sokutei, Japan) and thickness was measured.

3.5.2 Crushing strength (H)

Ten tablets were taken and the crushing strength of the tablets was determined by using hardness tester (Pharma test, PTZ-E, Germany). Each tablet was placed between two anvils, and the crushing strength that just caused the tablets to break was recorded. The average crushing strength of ten tablets was recorded.

3.5.3 Friability determination (f)

Ten tablets were weighed and placed in a plastic chamber of the friabilator (ERWEKA type TAR-20, Germany) attached to a motor revolving at a speed of 25 rpm for 4 min. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

3.5.4 Disintegration time (DT)

DT test was carried out based on the USP specification (USP 38/NF 33, 2015). Six tablets were placed in the basket rack assembly of a disintegration tester ((Medicinal equipment co., Ltd., UK), and were tested for disintegration in 900 ml of distilled water maintained at 37± 2^{o}C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh.

3.5.5 Standard calibration curve for paracetamol and determine content uniformity

Paracetamol content of the tablets was determined by UV/Vis spectrophotometric method based on standard calibration curve. Stock solution containing 0.2 mg/ml of paracetamol in phosphate buffer of pH 5.8 was prepared and diluted to six different concentrations (0.002, 0.004, 0.006, 0.008, 0.010, 0.012 mg/ml). UV absorbance readings were taken at 243 nm by using UV/visible spectrophotometer (JENWAY, 6505, England). The phosphate buffer solution was used as a blank. The Beer-Lambert curve was drawn and its correlation coefficient was calculated using equation 3.15 (USP 38/NF 33, 2015).

$$\%\ \text{Drug content} = \frac{\text{Absorbance of sample} * \text{average weight of tablet}}{\text{Absorbance of standard} * \text{weight of sample}} x100 \ldots\ldots\ldots\ldots (3.15)$$

3.5.6 In vitro drug release studies

The release profile of the paracetamol tablets were determined using Type II dissolution testing apparatus (DT600, ERWEKA, Germany) according to the ((USP 38/NF 33, 2015)). The dissolution medium was 900 ml of phosphate buffer of pH 5.8 maintained at a temperature of 37 ± 0.5°C and 50 rpm. From each experiment, 10 ml of sample was withdrawn at 5, 10, 15, 30, 45 and 60 min and replaced with equal volume of fresh medium at the same temperature to maintain sink condition. Samples were filtered using filter paper and absorbance was measured using UV/visible spectrophotometer in triplicate at 243 nm after appropriate dilution with the phosphate buffer of pH 5.8. Percent drug release was calculated from standard calibration curve.

3.6 Statistics

Statistical analysis to compare the effects of binders on the mechanical and release properties of paracetamol tablets was done using SPSS version 25 and one-way analysis of variance (ANOVA). Tukey multiple comparison test was used to associate the differences between some properties of the different batches (F1-F12) of granules and tablets. Moreover, Origin 8.5® (Origin Lab Corporation, Northampton, USA) software was used to plot figures. At 95% confidence interval, *P* values less than or equal to 0.05 were considered significant. All the values are specified as mean and standard deviation.

4. RESULTS AND DISCUSSION

4.1 Physicochemical characterization of *S. setigera* gum

The gum was purified using water and ethanol 90% (v/v) as solvents. The yield of the purified gum from exudates of *S. setigera* was found to yield about 60%. This value was lower than previous study obtained from *Melia azedarach* Gum (67.8 %). But the yield was higher than *Albizia* gum (39.38%) (Owusu, et al., *2022*). The isolated gum powder was brown, odorless and tasteless.

A 10% solution of the gum of *S. setigera* did not show bluish or reddish color upon the addition of iodine TS, this showed that there is no starch and dextrin, respectively, in the pure gum. Moreover, no blackish color or precipitate was formed when ferric chloride TS was added, implying that the absence of tannins in the gum. Table 2 shows some of the physicochemical properties of the gum. The swelling property of *S. setigera* gum was studied in distilled water, and it has high swellability. A similar study was done on *Melia azedarach* gum also has maximum swellability (Owusu, et al., *2022*).

Table 2: Physicochemical properties of *S. setigera* gum

Physicochemical parameter	Characteristics
Color	Brown
Odor	Odorless
Taste	Tasteless
Melting range	260-270°C
pH (1% solution)	4.7± 0.31
Tannin content	Absent
Starch and dextrin content	Absent
Viscosity (1%)	108.8± 0.45 cPs
Swelling power (ratio)	0.66 ± 0.03
Water solubility index (%)	40 ± 1.06
Loss on drying (%)	11.11± 0.12
Total ash (%)	7.8± 0.53
Water soluble ash (%)	0.071± 0.01
% Yield	60.0 ± 0.12
Microbial count (CFU/g) *	no colony of microbe

The *Sterculia* gum treated with water swelled into a mucilaginous gel. It was insoluble in ethanol but formed viscous sols in 60% hydro-alcoholic solutions. The moisture content of the gum was 11.11%, which is within the pharmacopeial specification (maximum of 15%) (BP, 2009). It is essential to investigate the moisture content of a material because the economic importance of an excipient for industrial application lies not only in the cost and easy availability of the biomaterial but also in the optimization of formulation processes such as drying, packaging and storage (Vehring, 2008).

The total Ash value of the *S. setigera* gum was 7.8% w/w which is higher than acacia 3.10% (Schmitt, *et al.*, 1999). Ash values show the level of adulteration or handling of excipients. Impurity by sand or earth is immediately noticed as the total ash is usually composed of inorganic mixtures of carbonates, phosphates, silicates and silica (Ohwoavworhua and Adelakun, 2005). There was no colony of *E. coli, S. aureus, S. aeruginosa* and *Salmonella* in the culture medium.

The pH of an excipient is an important parameter in determining its suitability in formulations, since the stability and physiological activity of most preparations depend on pH (Suvakanta, 2014). The pH of the gum solution (1% w/v) at a temperature of 25 ºC was 4.7± 0.31. This indicates that *S. setigera* gum is acidic in nature. This is expected as *S. setigera* gums are generally macromolecular acids (Odeku and Fell, 2004). Compared to acacia, the results obtained show that the pH of *S. setigera* gum is higher than the value (pH=4.4) reported for *Acacia senegal* gum (Siddig, 2003).

4.2 Relative solubility of the gum

Solubility values presented in Table 3 show that the gum is sparingly soluble in hot water and cold water but it has swellable nature. The *S. setigera* gum is insoluble in organic solvents (acetone, chloroform and ethanol). The insolubility of the gum is due to the nature of macromolecules. And the presence of acetyl group in the structure

In contrast, a study done in India stated that *S. setigera* gum is soluble in hot and cold water but insoluble in acetone, chloroform and ethanol (Sahu, 2019). This might be because different species of *S. setigera* have different solubility characteristics.

Table 3: Solubility of the *S. setigera* gum in different solvents (n = 3, mean ± SD).

Solvent	Solubility (g/ml)	Solubility (%)
Cold distilled water	0.0030±0.00024	0.300±0.024
Hot distilled water	0.0061±0.0004	0.610±0.040
Ethanol	0.0014±0.0001	0.140±0.010
Acetone	0.0000±0.0000	0.000±0.000
Chloroform	0.0001 ± 0.00001	0.010±0.001

4.3 Moisture sorption-desorption property

The water sorption-desorption result presented in Figure 2, showed that about 1.6% of water was absorbed which was not much significant amount. In the presence of a desiccant, the water was also rapidly lost within a few days. Similar trend was observed with cashew gum (Zakaria, and Zainiah, 1996).

The implication of this was that the gum, when stored in damp environment cannot be easily susceptible to microbial and physicochemical deterioration. Hence, the integrity of the gum can be maintained if the gum is store at room temperature.

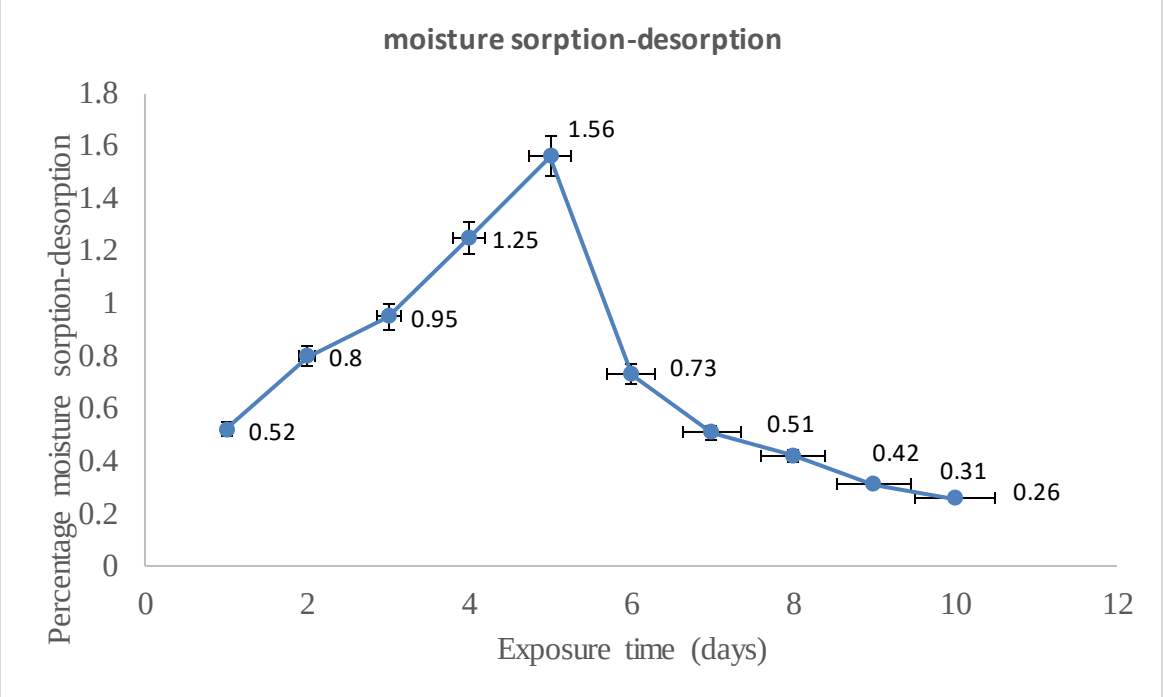

Figure 2: Percent of moisture sorption-desorption pattern of *Sterculia* gum powder (n=3).

4.4 Viscosity of the gum

High viscous gums have better quality than less viscous gums for use as a binder and matrix forming agent (Franz, 1986). Viscosity of the aqueous dispersions of *Sterculia* gum increased with increase in gum concentration. The mean viscosity values increase as the concentration increase but after some time not much increased. The gum had significantly higher viscosities than the respective concentrations of PVP and acacia ($p < 0.05$).

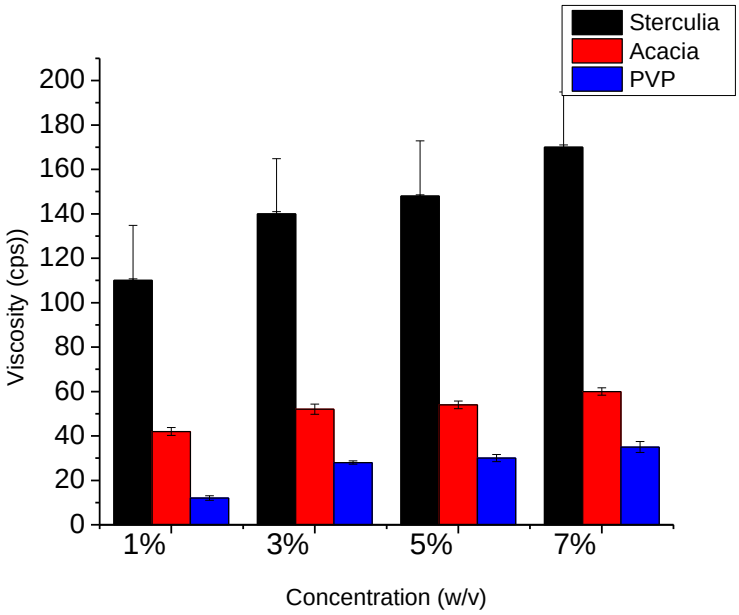

Figure 3: The effect of concentration on the viscosity of the *sterculia* gum, acacia and PVP at 25 °C.

4.5 X-Ray Diffraction

X-ray powder diffraction (XRD) is a powerful nondestructive technique and a rapid analytical technique primarily used for phase identification and characterization of crystalline materials and can provide information on unit cell dimension (Ivanisevic et al., 2010). The X-ray diffraction pattern of *S. setigera* gum is depicted in Figure 4. The diffractogram shows that *S. setigera* gum has a peak without any distinct sharp diffraction peaks. *S. setigera* gum was showed that amorphous structure with low overall crystallinity due to broader peak and have no sharp peak. Similar studies were done on almond gum and cashew gum, which showed that the gum was an amorphous nature (Bashir and Haripriya, 2016, Zakaria, and Zainiah, 1996).

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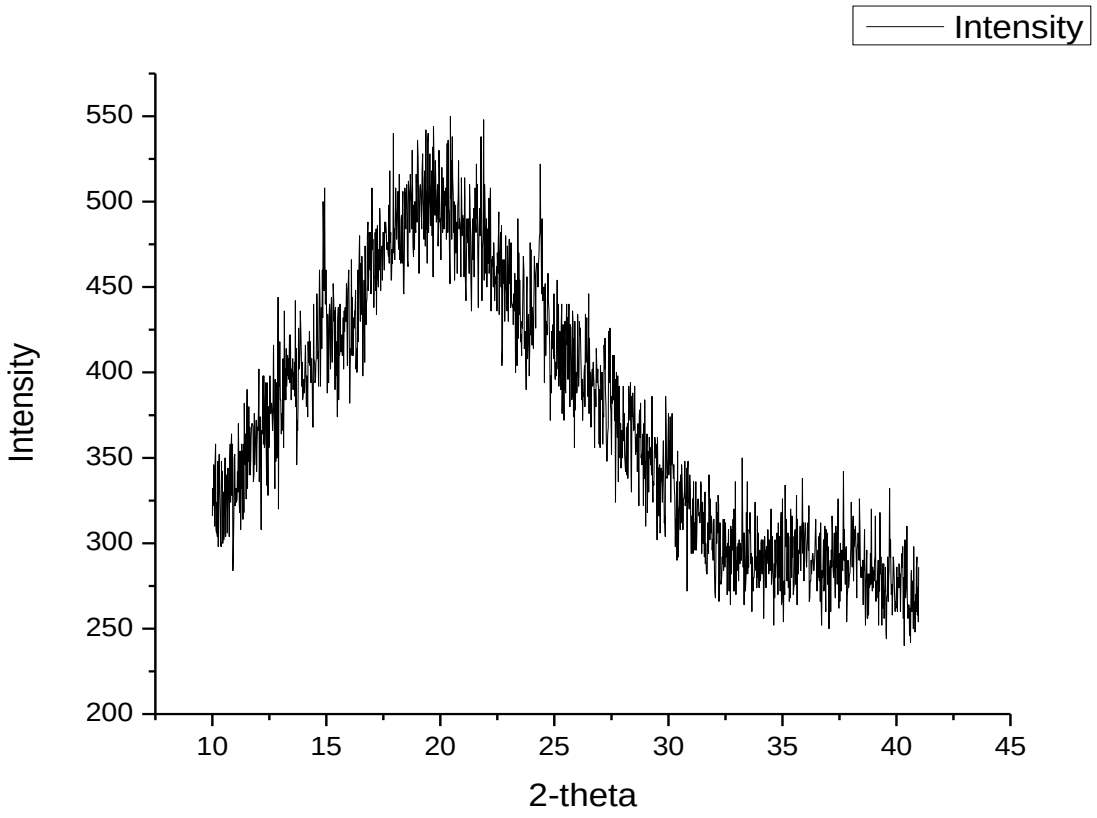

Figure 4: X-ray powder diffractogram of *S. setigera* gum

4.6 Density and related properties of the gum powder

Density and density related properties of the gum powder are indicated in Table 4. The Carr's index and Hausner ratio of the gum were 28.57% and 1.4, respectively. This indicates that the gum powder is less flow able. Adjustment of formulations containing *Sterculia* gum for the improvement of flow properties during such process development will be necessary (Singh *et al.*, 2010).

The bulk and tapped densities give an insight on the packing arrangement of the particles and the compaction profile of the material. The Carr's index and Hausner ratio are the measures of the tendency of a powder to be compressed. As such, they are measures of the relative importance of interparticle interactions. In a free-flowing powder, such interactions are generally less significant, and bulk and tapped densities were closer in value.

For poorly flowing materials, there are frequently greater interparticle interactions and greater alteration between bulk and tapped densities. These deviations are reflected in Carr's index and Hausner ratio (USP 38/NF 33, 2015).

Table 4: Density and density related properties of the *Sterculia* gum powder (n=3, mean± SD

Variables	Values
Bulk density (g/ml)	0.45±0.020
Tapped density (g/ml)	0.63 ± 0.036
Carr's index (%)	28.57
Hausner ratio	1. 4

4.7. Characteristics of granules

4.7.1. Moisture Content of paracetamol granules

In order to maintain good compressibility and tablet properties with optimum tensile strength, the moisture content of paracetamol granules prepared with *S. setigera* gum as binder were determined and found to be between 1.5-3.0%. It has been reported that the moisture content of granules influences tablet hardness. Although, not a proportional relationship, it can be seen from Figure 5 that moisture content in general shows an increasing pattern with increased concentration of the binders.

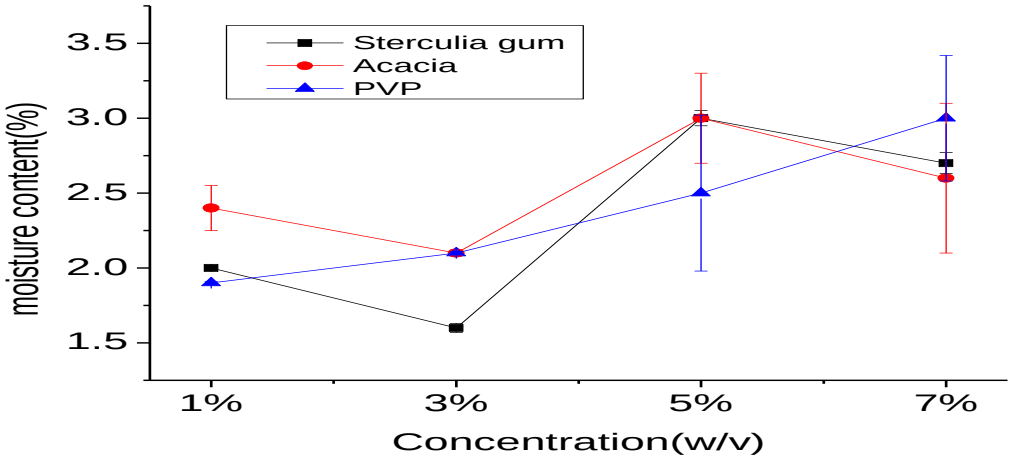

Figure 5: Moisture content of granules prepared by *S. setigera* gum, acacia and PVP as binders.

4.7.2. Granule size distribution

Granule size distributions at different binder concentrations are shown in Table 5. Generally, good granule particle size distributions were obtained for all the binders used. However, an increased in proportion of larger granules was observed with increased binder concentration. An increase in mean granule size was also noted with increase in binder concentration of *S. setigera* gum. This growth in granule size may be attributed to an increase in binding capability of the aqueous binder solution. The order of average granule size was Acacia> PVP>*Sterculia* gum with respective concentration.

Granule particle size can influence the quality of solid dosage forms. Any interference with the uniformity of fill volumes may alter the mass of drug incorporated into the tablet and this reduces the content uniformity of the drug. Therefore, a normal particle size distribution is essential to decrease weight variation and sustain content uniformity (Shekunov, 2007).

Table 5: Size distribution of paracetamol granules prepared with different binder concentrations.

Formulation	Weight retained and percent retained/(micrometer) sieve opening				
	710/315(512.5)	315/224(269.5)	224/115(169.5)	115/0 (57.5)	Average granule size (micrometer)
F_1	7.86(26.34%)	8.36(28.02%)	4.32(14.47%)	9.3(31.16%)	252.95
F_2	6.69(22.44%)	10.84(36.36%)	3.33(11.17%)	8.95(30.02%)	249.18
F_3	9.54(32.40%)	7.68(26.09%)	2.49(8.46%)	9.73(33.05%)	269.7
F_4	9.93(33.17%)	8.4(28.06%)	2.13(7.12%)	9.48(31.77%)	275.95
F_5	9.68(32.42%)	8.96(30.02%)	2.43(8.14%)	8.78(29.41%)	277.76
F_6	10.74(36.22%)	8.66(29.20%)	2.43(8.20%)	7.82(26.37%)	293.38
F_7	12.23(41.02%)	9.03(30.30%)	2.34(7.85%)	6.21(20.83%)	317.17
F_8	13.46(45.20%)	8.22(27.60%)	1.76(5.90%)	6.35(21.31%)	328.28
F_9	7.94(26.65%)	9.69(32.53%)	2.78(9.33%)	9.38(31.49%)	258.16
F_{10}	10.68(35.81%)	9.36(31.40%)	2.37(7.95%)	7.41(24.85%)	295.91
F_{11}	9.38(31.44%)	9.23(30.94%)	2.8(9.40%)	8.42(28.22%)	276.67
F_{12}	10.14(34.10%)	8.43(28.34%)	2.43(8.17%)	8.75(29.41%)	281.89

4.7.3. Bulk characteristics of granule

Bulk density of a granulation is primarily dependent on particle size, particle size distribution, and particle shape. It is an indirect measure of granule flow and determines the die fill volume. Granules having larger bulk density need comparatively lower die fill volume than those having smaller bulk density. As can be seen from Table 6, the bulk and tapped densities of the granules decrease with increasing concentration of binders. This could be attributed to the increase in the proportion of larger granules with increasing binder concentration. The larger granules occupy larger volume making the bulk density value lower than smaller granules occupying smaller bulk volume.

Table 6 shows that the granules have Carr's index less than 15% implying the granules have good flow property. The Hausner ratio was also observed to be less than 1.25. Measurement of granule flow rate is a direct method of determining granule flowability. There was no significant difference in the angle of repose of the different granules. The flow rate of the granules was found to decrease with increasing concentration of binder. This decrease in flow rate can be attributed to the increase in granule size with increasing binder concentration. Moreover, greater flow was observed in the denser granulations.

Table 6: Evaluation of the paracetamol granules

Formulation	Properties					
	BD (g/ml) *	TD (g/ml) *	CI (%)	HR	AR (^{o})	Flow rate (g/sec) *
F_1	0.5± 0.020	0.53±0.030	5.66	1.06	24.7	1.10±0.13
F_2	0.42±0.000	0.43±0.006	2.32	1.04	29.40	1.20±0.20
F_3	0.43±0.006	0.46±0.010	6.52	1.06	29.25	1.00±0.36
F_4	0.46±0.006	0.52±0.010	11.53	1.12	30.90	1.55±0.22
F_5	0.45±0.005	0.48±0.006	6.25	1.06	23.27	1.05±0.11
F_6	0.49±0.011	0.52±0.015	5.76	1.06	27.02	0.98±0.08
F_7	0.45±0.035	0.49±0.038	8.16	1.08	26.10	1.16±0.31
F_8	0.43±0.011	0.47±0.021	8.51	1.09	24.70	1.83±0.06
F_9	0.42±0.005	0.45±0.010	6.66	1.02	30.90	1.36±0.18
F_{10}	0.43±0.00	0.46±0.007	6.52	1.07	28.80	1.11±0.13
F_{11}	0.42±0.005	0.46±0.007	7.58	1.10	28.80	1.05±0.1
F_{12}	0.42±0.005	0.45±0.010	5.18	1.05	24.30	0.83±0.03

Values shown are mean ± SD (*n = 3). F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, and F12, Paracetamol granules prepared with 1, 3, 5 and 7% *Sterculia* gum (F1-F4); acacia *(F5-F8)* and (F9-F12) PVP as binders, respectively.

4.7.4. Granule friability

Granule friability is one indicator of the ability of a given binder to form compacted mass during the granulation process. It is the measure of granules resistance to dust upon an impact stress. During a granule friability test, the granules size might be reduced by attrition, i.e., removal of particle from the surface of the granule or by breakage or fragmentation of the whole granule. The results of the friability tests of the different batches of granules are shown in Table 7. As expected, the friability of the granules was found to decrease with increased binder concentration. And as the granule size decreases, friability of the granules was increased. Generally, the order of percent friability values were *S. Setigera* gum > Acacia gum > PVP.

Table 7: Friability data of the granules prepared with various binders at different binder concentrations.

Binder concentration (% w/w)	Friability (%)		
	Sterculia gum	Acacia	PVP
1%	3.00 ± 1.01	2.07± 0.63	1.92± 0.05
3%	2.57±0.05	1.60± 0.29	1.57± 0.35
5%	1.00± 0.60	1.25± 0.11	1.00±0.02
7%	0.85± 0.03	0.65± 0.27	0.70± 0.09

Mean ± SD (n = 3),

4.8. Structural analysis and drug-excipient interaction

FTIR spectroscopy is a quick and simple technique for identifying compounds. The FTIR spectrum of a given compound is unique and characteristic. This is because FTIR spectrum distinguishes between the different kinds of bonds and functional groups in a molecule (Coates, 2006). Principal peaks for paracetamol are at wave numbers 1506, 1657, 1565, 1263, 1227, 1612 cm^{-1} (Clarke, 2011). FTIR spectra of paracetamol, showed characteristic of O-H, N-H, C=O (amide) stretching bands at 3323.12 cm^{-1}, 3099.25 cm^{-1}, 1652.88 cm^{-1}, respectively. Whereas, amide group, C-N-H group and aromatic rings at 1562.23 cm^{-1}, 1259.43 cm^{-1} and 837.05 cm^{-1}, respectively, were also observed (Bashar, 2010).

In the present study, interactions between the *S. setigera* gum and paracetamol have been studied. The FTIR spectra showed in (Figure. 6, 7, and 8) demonstrate spectra of *S. setigera* gum, Paracetamol, and Paracetamol with *S. setigera* gum, respectively. When the spectra are compared, it was found that there was no major interaction between the gum and paracetamol as there were no distinct changes in the peaks of paracetamol. These major peaks of paracetamol in FTIR spectrum of the mixture were not altered suggesting there was no significant interaction between paracetamol and *S. setigera* gum.

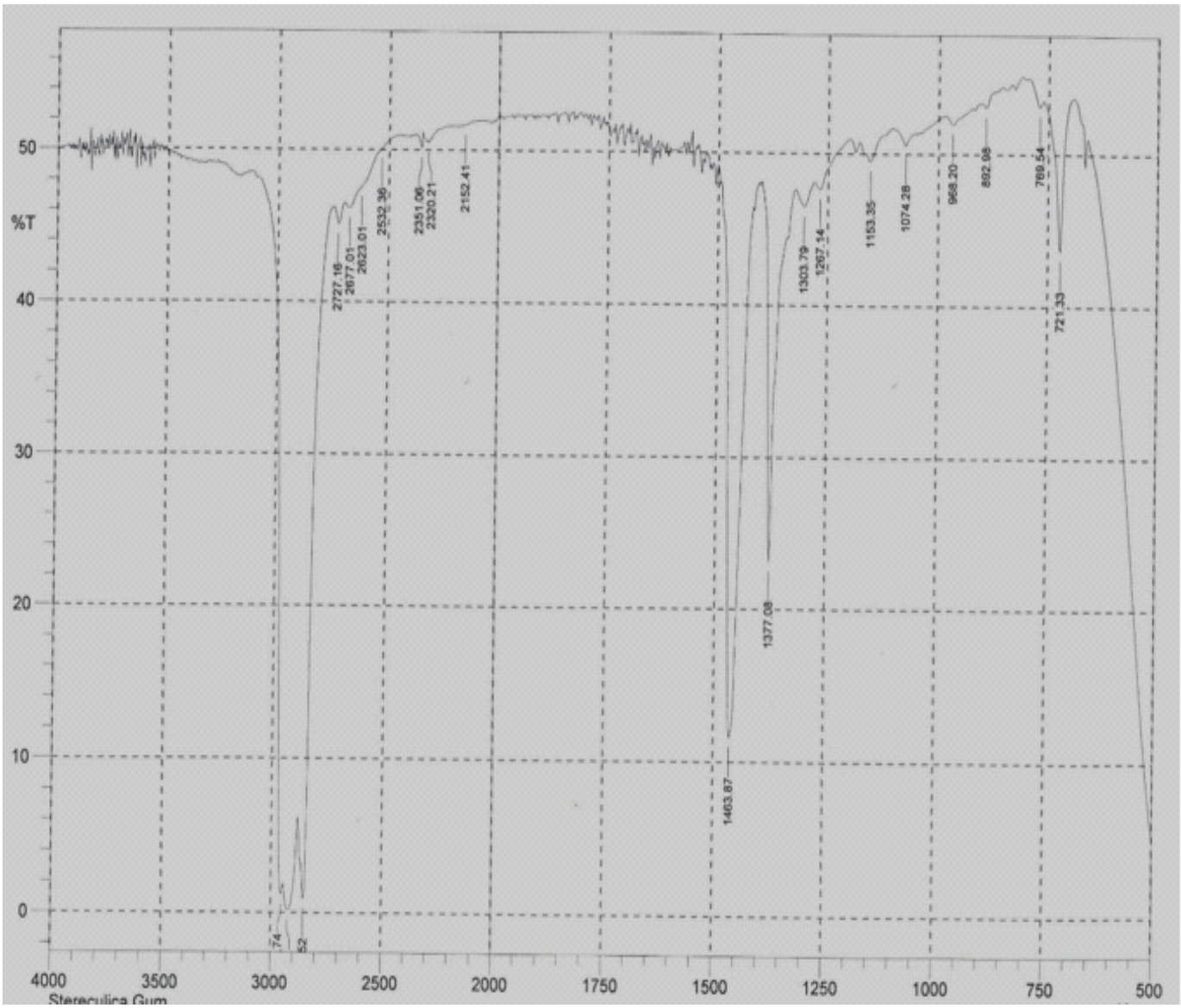

Figure 6: FTIR spectrum of *S. setigera* gum

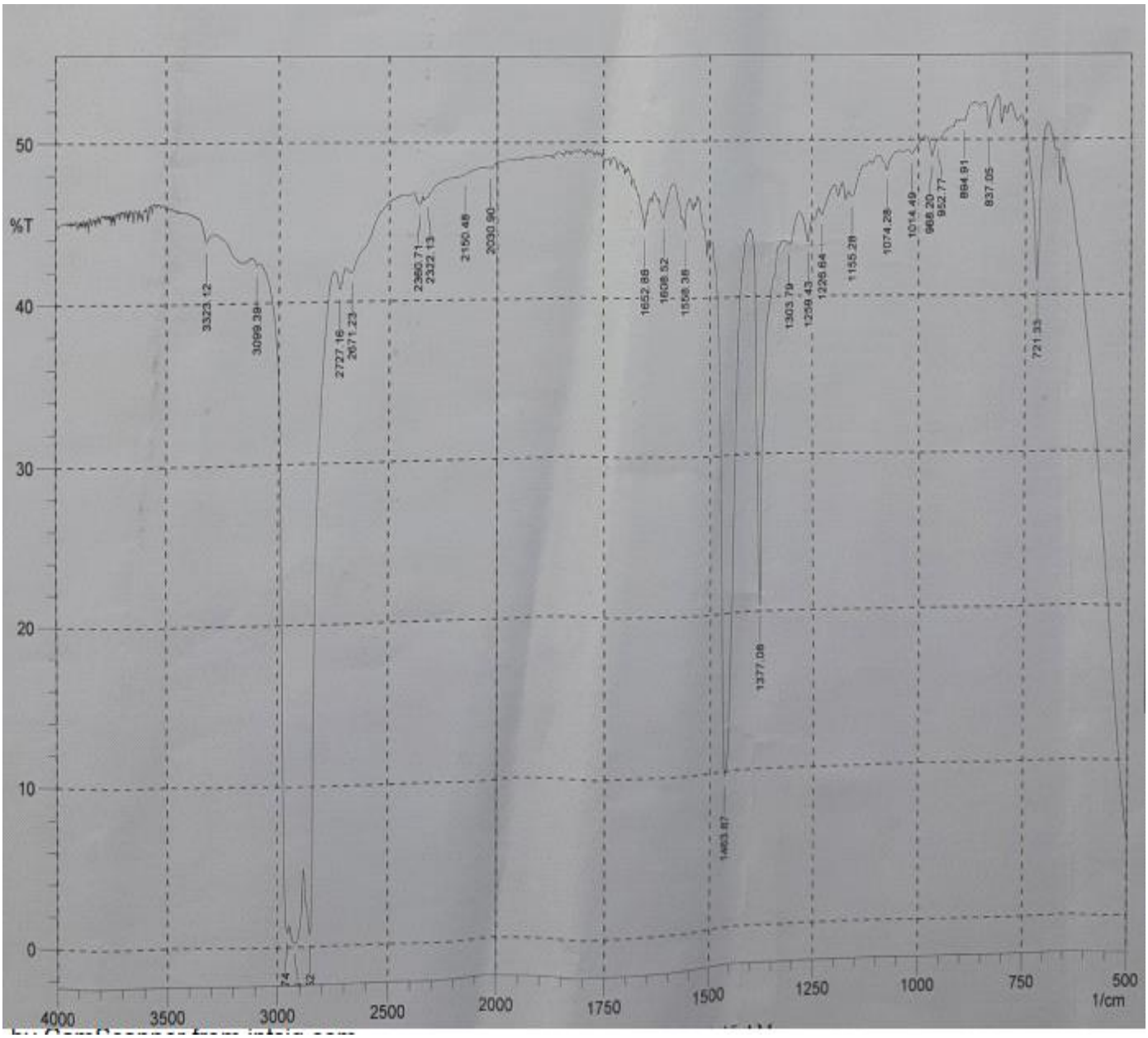

Figure 7: FTIR spectrum of pure paracetamol powder

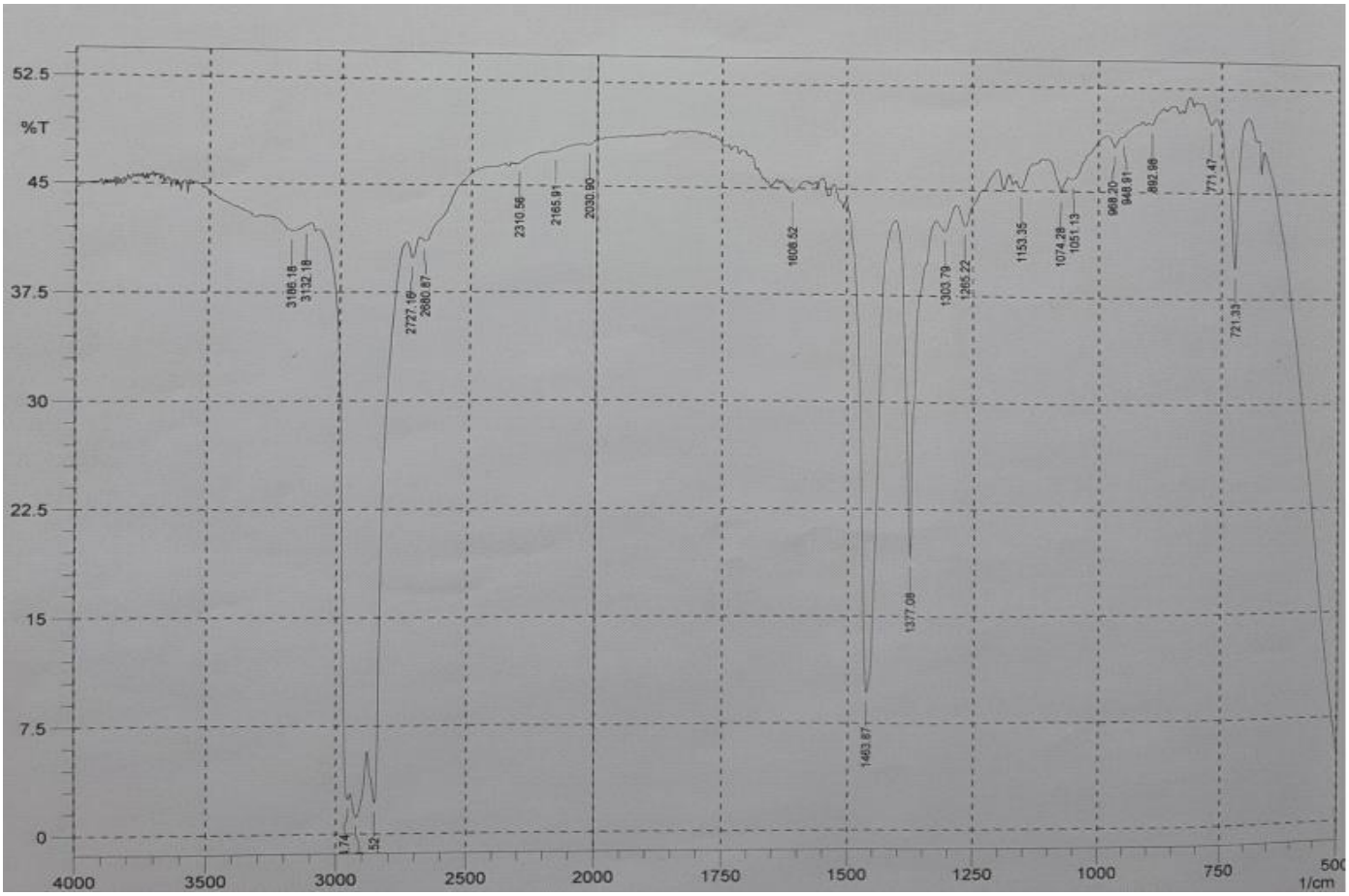

Figure 8: FTIR spectrum of paracetamol and *S. setigera* gum mixture.

4.9 Tablet properties

4.9.1 Weight uniformity and thickness

Uniformity of weight is an indication of the amount of API in a batch of tablets. However, these do not assure that the API is uniform in all tablets especially in formulations with low doses. Furthermore, if weight, thickness or diameter of tablets in a batch varies, there would be variations in disintegration and dissolution. The compendia specification for weight uniformity states that for tablets weighing more than 324 mg, weights of not more than two tablets should deviate from the average weight greater than 5% (USP 38/NF 33, 2015).

All the tablets have a diameter of 12.5 ± 0.56 mm which was already fixed by the diameter of the die cavity of the tablet machine. Weight uniformity and thickness of tablets are given in Table 8. The weight of the tablets prepared using different binders with various concentrations met the compendia specification and it has no significant difference in these values.

Table 8: Mean weight and thickness of the different formulations of paracetamol tablets (n=20, mean ± SD).

Formulation	Weight (g) (mean ± SD)	Thickness (mm) (mean ± SD)
F_1	649.00 ± 2.13	5.76 ± 0.06
F_2	650.66 ± 1.04	5.75 ± 0.10
F_3	650.00 ± 3.00	5.79 ± 0.09
F_4	650.71 ± 1.92	5.80 ± 0.09
F_5	647.33 ± 0.52	5.76 ± 0.15
F_6	648.00 ± 1.51	5.78 ± 0.01
F_7	648.65 ± 2.08	5.78 ± 0.10
F_8	650.00 ± 1 .02	5.76 ± 0.12
F_9	647.66± 2.08	5.79 ± 0.12
F_{10}	646.89± 2.52	5.78 ± 0.02
F_{11}	648.66± 0.63	5.76 ± 0.08
F_{12}	650.31±1.15	5.77 ± 0.03

All the values are expressed as mean ± SD

4.9.2 Crushing strength

Hardness shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. It is the property of a tablet that is measured to assess its resistance to permanent deformation. Furthermore, the mechanical strength of a tablet determines the disintegration time and the rate of dissolution. As the concentration of the binder increases, the mechanical strength increases (Allen *et al*., 2004). The relationship between binder concentration and crushing strength as well as friability for all formulations at a constant disintegrant concentration (corn starch) are shown in Table 9. The crushing strengths of tablets prepared with *S. setigera* gum < Acacia < PVP K-30.

4.9.3. Friability

Friability decreased with increasing percentage of binders. Friability is especially important because the tablet is subjected to various abrasive motions during production, packaging, distribution and use (Adebayo & Itiola, 2003). As shown in Table 9, paracetamol tablets prepared with 1% of *S. setigera* gum and Acacia failed to meet the friability test (>1%)(USP 38/ NF 33., 2015). Tablets prepared at concentrations of more than 3% of *S. setigera* gum met the compendial specifications for friability with values comparable to acacia but slightly higher than PVP. This suggests that at 3% concentration and above, the gum can keep the tablets intact and withstand abrasive motions during handling and transportation.

4.9.4. Disintegration tests

Disintegration is the rate-limiting step for immediate-release formulations. Because of that dissolution rate can be increased by the quick breakup of the tablet into fine particles. The nature of tablet hardness affect the disintegration time. The nature of additive highly affected disintegration time. In general, as the binder concentration increases the disintegration time increased. Prolonged disintegration time could be attributed to the gum resulting in extensive plastic deformation, leading to improved contact angle between particles, and reducing rate of water penetration into interstitial void spaces. This resulted in reduced swelling of the disintegrant and disruption of the tablets and at the same time prolonged disintegration time (Odeku & Itiola, 2003).

The disintegration profile of the tablets prepared with different concentrations of binders is shown in Table 9. The observed disintegration time of F_4 does not meet the standard. High concentration of Sterculia gum prolongs disintegration time, which could be ideal for delayed-release formulations.

4.9.5. Content uniformity

The content uniformity characteristics showed that the tablets produced with the *S. setigera* gum show an acceptable content profile within the range of its concentration in tablets.

Table 9: Physical parameters of paracetamol tablets prepared with *S. setigera* (F_1-F_4), acacia (F_5-F_8) and PVP-K30 (F_9-F_{12}) as binders.

Formulation	Hardness (N)	Friability (%)	Disintegration time(min)	Content uniformity (%)
F_1	42.20±0.61	1.24 ±0.34	2min35sec	99.67±0.25
F_2	54.25±1.47	0.92±0.20	9 min.30sec	99.53±0.08
F_3	93.20±0.20	0.75±0.14	11min.50sec	98.06±0.64
F_4	113.40±2.90	0.56±0.12	17 min.00sec	100.20±1.90
F_5	56.21±1.30	1.40±0.04	4 min.30sec	98.00±2.30
F_6	65.33±1.08	0.87±0.21	6 min.30sec	97.67±0.84
F_7	106.53±2.64	0.64±0.06	6 min.25sec	98.70±1.28
F_8	118.41±4.22	0.46±0.14	9 min.30sec	101.50±0.71
F_9	85.35±2.11	0.78±0.07	2 min.20sec	98.00±0.94
F_{10}	104.60±3.09	0.57±0.20	3 min.00sec	99.25±0.07
F_{11}	110.46±2.70	0.80±0.16	2 min.00sec	96.24±1.36
F_{12}	108.20±1.59	0.44±0.08	3 min.16sec	99.50±1.01

Values shown are mean ± SD (n = 3). F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, and F12, Paracetamol tablets prepared with 1, 3, 5 and 7% *Sterculia gum* (F1-F4) and acacia gum (F5-F8) and PVP (F9-F12) as binders, respectively.

4.9.6. Calibration curve

The calibration curve of paracetamol reference standard (Figure. 9) in phosphate buffer of pH 5.8 at 243 nm at six different concentrations yielded a linear curve with a regression equation of A = 0.1271C - 0.0167 and R^2 = 0.9993 (where, A is the absorbance and C is the concentration in µg /ml).

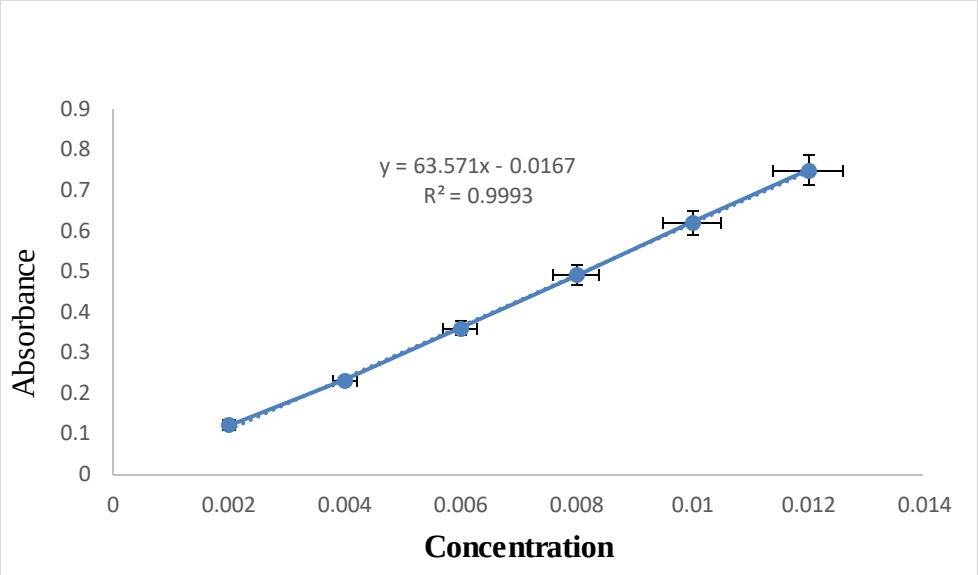

Figure 9: Calibration curve of paracetamol reference standard in pH 5.8 phosphate buffer at 243 nm (r^2 = 0.9993).

4.9.7. *In vitro* drug release

In vitro drug release profiles of the tablets prepared with different concentrations of binders are presented in Figures 10-12. As the binder concentration increased, there was a general decrease in the release rate of paracetamol from the tablets. This might be attributed to the sticky film of hydration on the surface that occurs at high binder concentrations reducing the drugs diffusion. The *S. setigera* gum showed less drug release rate than acacia gum and PVP. Figure 12 reveal that tablets made with PVP provide the highest drug release. The gum at higher concentrations produced tablets with a dense matrix, which is highly resistant to drug release from the formulations. Tablets prepared with PVP as a binder showed significantly higher dissolution profiles than acacia and *S. setigera* at the respective concentrations ($p < 0.05$).

Batch F-3 release showed 72% of drug releases at the end of 30 min, which is lower than F-7 formulation, which showed 75% drug release at the end of 30 min. Batch F4 release showed 77% of drug releases at the end of 30 min, which is higher than F8 formulation, which showed 72% drug release at the end of 30 min. Batch F-10 showed 81% drug release at the end of 30 min while batch F-2 released 85% drug at the end of 30 min.

The drug release profile of the tablets showed that tablets prepared with PVP exhibited high release profile than Acacia and *S. setigera* gum binder.

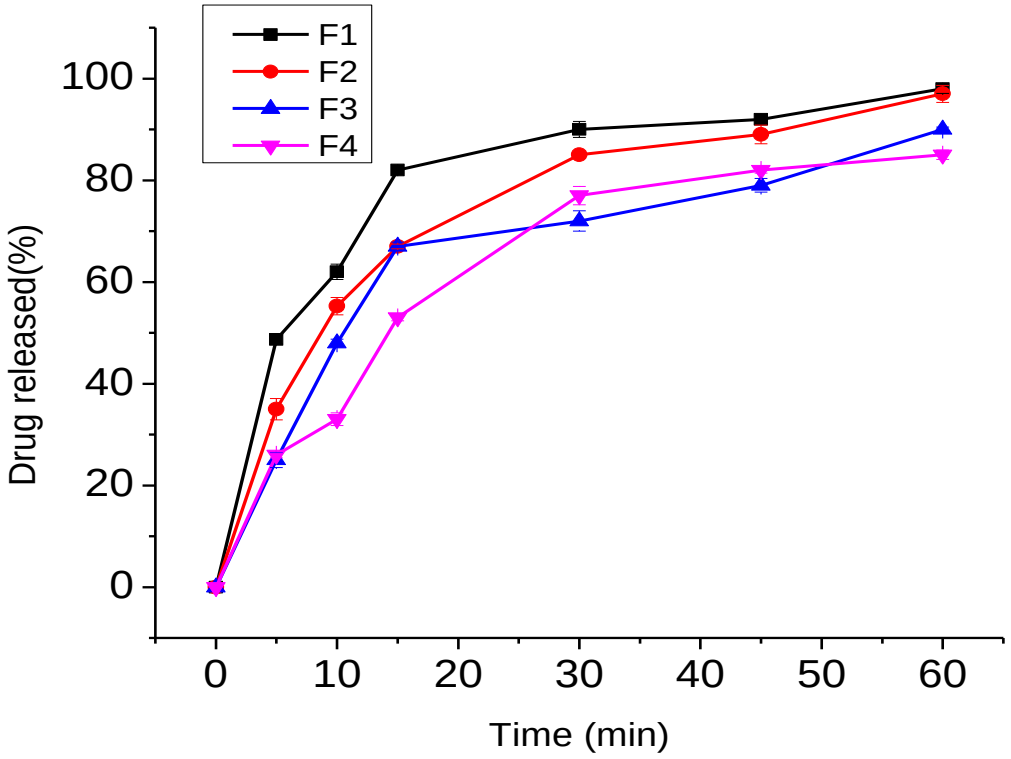

Figure 10: *In vitro* release profile of paracetamol from tablets prepared with *Sterculia* gum as binder

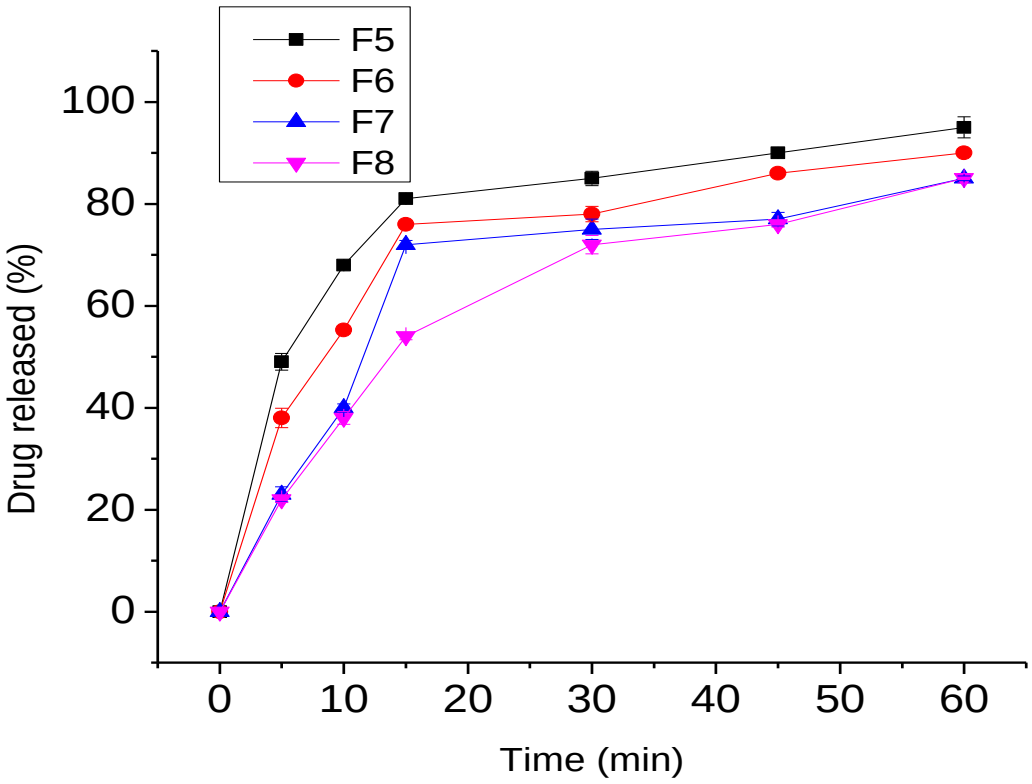

Figure 11: *In vitro* release profile of paracetamol from tablets prepared with Acacia (F5-F8) as binder.

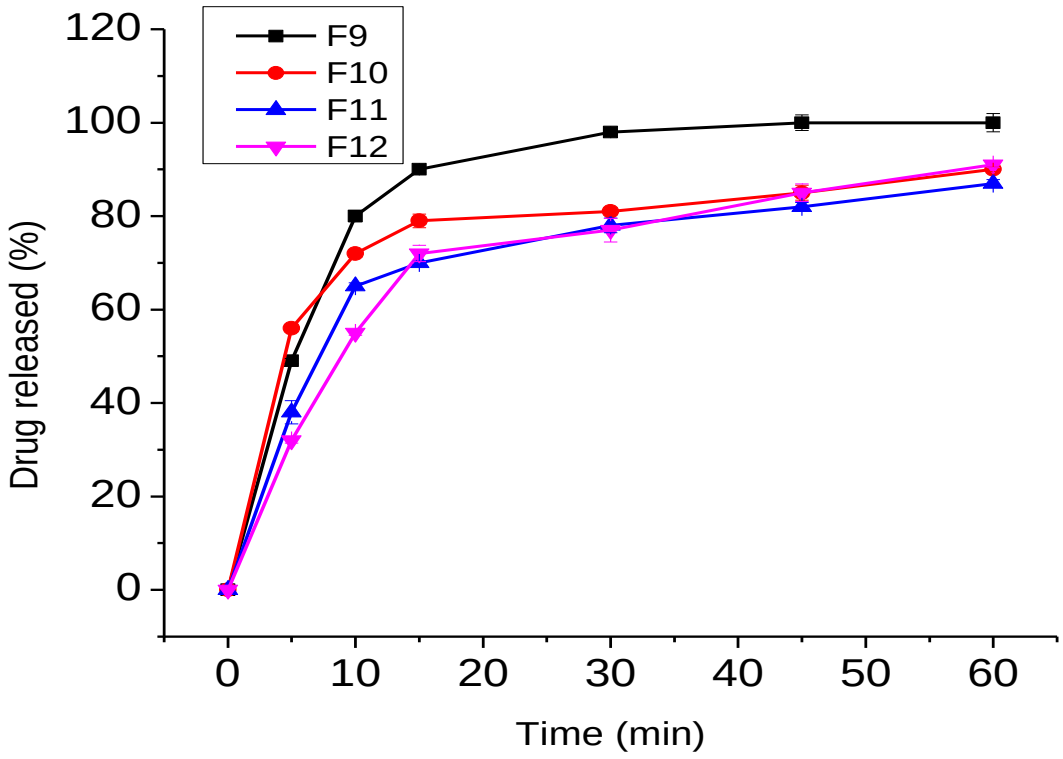

Figure 12: *In vitro* release profile of paracetamol tablets prepared with PVP as a binder.

5. Conclusions

Sterculia gum is non-toxic, biodegradable and biocompatible excipient that can be employed as tablet binding agents this study provided insight in the evaluation *S. setigera* gum as a binder in tablet formulations using paracetamol as a model drug.

The granule prepared *Sterculia* gum had good flowability and compressibility with the less variability in weight. Using the *S. setigera* gum resulted in a suitable quality granule with a uniform size distribution, and high friability with increasing binder concentrations comparable to those prepared with reference binders. Tablets prepared with the *S. Setigera* gum showed lower crushing strengths than those prepared with the reference binders. Regarding the disintegration time, tablets with *S. setigera* gum had higher disintegration times than those prepared with PVP and Acacia.

The drug release studies of the tablets indicated that tablets prepared with *Sterculia* gum exhibited less drug release profile than Acacia and PVP. Hence, *S. setigera* gum could be used as a binding agent for tablet formulations.

6. Suggestions for further studies

The results of this study suggest further investigation in the following directions:

- Detailed physicochemical characterization of *Sterculia setigera* gum and morphological characterization should be addressed;
- Stability studies of the tablets prepared with the *Sterculia* gum should be evaluated;
- Further chemical analysis of *Sterculia* gum should be done
- The application of *Sterculia* gum in food industries should be investigated.

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