CHAPTER 4

COST- EFFECTIVE NATURAL BINDER EFFICIENCY

4.1 FORMULATION AND EVALUATION OF EFFERVESCENT TABLETS

The oral dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and thus onset of action is prolonged. This can be overcome by administrating the drug in liquid from but, many APIs have limited level of stability in liquid form. So, Effervescent Tablets acts as an alternative dosage form. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO$_2$ in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water. Due to liberation in CO$_2$ gas, the dissolution of API in water as well as taste masking effect is enhanced. The advantages of effervescent tablets compared with other oral dosage forms includes an opportunity for formulator to improve taste, a more gentle action on patient’s stomach and marketing aspects. The formulation of tablets can be done by using direct compression, wet granulation as well as dry granulation. Due to its good effervescent reaction there is no problem in capping.

4.1.1 Effervescent Tablet

To manufacture these tablets, either wet fusion or heat fusion is adopted. The tablets are compressed soft enough to produce an effervescent
reaction that is adequately rapid. Water soluble lubricants are used to prevent an insoluble scum formation on water surface. To add sweetness to the formulation, saccharin can be added since sucrose is hygroscopic and add too much of bulk to the tablet. The manufacturing shall be done under controlled climatic condition to avoid effervescent reaction. The packaging is done under 25% RH at 25ºC. Hands of the consumers and atmospheric moisture after opening the container can also result in loss of product quality. The most commonly used effervescent tablet today is aspirin tablet.

4.1.2 Consideration in Effervescent Tablets Formulation

There are several factors, which influence the release of drug from effervescent tablets.

1. Particle size
2. Dose
3. Solubility

4.2 REASON FOR SELECTION OF EFFERVESCENT TABLETS OF PARACETAMOL

- **Fast onset of action** - Effervescent tablet have major advantage that the drug product is already in solution at the time it is consumed. Thus the absorption is faster and more complete than with conventional tablet. Faster absorption means faster onset of action. Effervescent drug are delivered to the stomach at a pH that is just right for absorption. Many medication travel slowly through the gastrointestinal tract or have absorption that is hampered by food or other drug.

- **No need to swallow tablet** - Effervescent medications are administered in liquid form so they easy to take as compared
to tablets or capsule. The number of people who cannot swallow tablet or who dislike swallowing tablet and capsule is growing. With an effervescent dosage form, one dose can usually delivered in just 3 or 4 ounces of water.

- **Good stomach and intestinal tolerance** - Effervescent tablet dissolve fully in a buffered solution. Reduced localized contact in the upper gastrointestinal tract leads to less irritation and greater tolerability. Buffering also prevent gastric acids from interacting with drug themselves, which can be a major cause of stomach.

- **More portability** - Effervescent tablet is more easily transported than liquid medication because no water is added until it is ready to use.

- **Improved palatability** - Drugs delivered with effervescent base, taste better than most liquids, mixture and suspensions. Superior taste masking is achieved by limiting objectionable characteristics and complementing formulations with flavor and fragrances. The effervescent tablet essentially include flavoring so they taste much better than a mixture of non-effervescent powder in water. Moreover they produce fizzy tablets, which may have better consumption appeal than the traditional dosage form.

- **More consistent response** - Drugs delivered with effervescent technology have predictable and reproducible pharmacokinetics profiles that are much more consistent than the tablets or capsule.
• **Accurate dosing** - Researchers have been shown that effervescent tablets enhance the absorption of number of active ingredients compared to conventional formulations. This is because the carbon dioxide created by the effervescent reaction can enhance active ingredient permeability due to an alteration of paracellular pathway. The paracellular pathway is the primary route of absorption of hydrophilic active ingredients in which the solutes diffuse into the intercellular space between epithelial cells. It is postulated that the carbon dioxide widens the intercellular space between cell which leads to greater absorption of active ingredients (both hydrophilic and hydrophobic). The increased absorption of hydrophobic active ingredients could be due to the non-polar carbon dioxide gas molecules thus creating an increased hydrophobic environment, which would allow the hydrophobic active ingredients to be absorbed.

Conventional tablets are often associated with slower onset of action and also undergoes first pass metabolism. Effervescent tablet avoid the first pass metabolism and also produce rapid onset of action. Oral liquid also provide rapid onset of action but required carefully handling. Slower onset of action and also undergoes first pass metabolism. Effervescent tablet avoid the first pass metabolism and also produce rapid onset of action. Oral liquid also provide rapid onset of action but required carefully handling.

### 4.3 MANUFACTURING METHODS OF TABLETS

In early days, most of the tablets required granulation of the powdered Active Pharmaceutical Ingredient (API) and Excipients. The availability of new excipients, modified form of old excipients, invention of
new tablet machinery and modification of old tablet machinery provides an ease in manufacturing of tablets by simple procedure of direct compression. Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering advantage in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

Tablets are the most popular dosage form for pharmaceutical products for therapeutic use. Tablets are prepared by compressing a powder mixture in a die at high compression force. The powder mixture contains next to the drug generally also filler binders, disintegrants, lubricants, glidants etc. The large scale production of high quality tablets requires a tablet mixture with excellent properties regarding homogeneity, flowability and compactibility. When the powder mixture does not possesses these properties it has to be preprocessed, else direct compression can be used.

4.4 TABLET MANUFACTURING

There are 3 main methods of producing tablets:

- **Direct Compression** - The drug itself is compressible and/or it can be mixed with a filler that is compressible (e.g. lactose).

- **Wet Granulation** - The powder mixture of the drug and excipients is granulated by wet methods prior to compression.

- **Dry Granulation** - The powder mixture of the drug and excipients is granulated by dry methods prior to compression.

With direct compression the powder mixture is blended during a period of time and can directly be compressed into tablets. Only a lubrication
step may be necessary to prevent the mixture from adhesion to the die and punches during compression. Direct compression can be used when the mixture already has good tableting properties of itself. The mixture has to flow easily and give good binding during compaction. Unfortunately, most tablet mixtures lack these properties and a wet granulation step is necessary.

With wet granulation, extra process steps are necessary to produce a tablet mass with sufficient tableting properties. The powder mixture is dry blended to give a homogeneous distribution of all the components in the mixture. Then a binder solution is added to the mixture to moisten the particles. By introduction of the solution, binding between the primary particles improves and stronger tablets can be produced. Mixing is continued until the granulation end point has been reached. The end point may be defined as the mixing time or amount of granulation liquid that produces a certain amount of granules with a specific diameter. The mass is screened to remove large lumps, and dried to remove the granulation liquid.

Finally, the granulations may be dry sieved to remove the agglomerates that were formed during drying. Just as with direct compression, lubrication of the granulations may be necessary. There are various techniques of producing granules such as dry and wet granulation, extrusion, or spray drying. Most commonly used is wet granulation. Here the aggregates are produced by agitation of moistened powders. This thesis deals with the wet granulation process as a preprocessing technique for the manufacturing of pharmaceutical tablets.

In all of these methods the active ingredient is usually mixed with other inactive ingredients (excipients). Excipients improve the physical properties of the tablet. Excipients are components of tablets that that have a role other than the therapeutic effect, they include:
• Fillers (diluents)
• Binders
• Disintegrants
• Lubricants, and glidants
• Preservatives
• Flavoring agents
• Film formers
• Opacifiers and colors

4.4.1 Direct Compression

In the direct compression method of tablet production, dry ingredients are thoroughly mixed and then compressed into tablets. This eliminates the drying steps associated with the wet granulation method. It also reduces the higher costs involved in wet granulation including increased equipment, labor, time, process validation and energy expenditure. As a result, direct compression is both efficient and economical, well suited to the production of high quality tablets, which exhibit hardness, low friability and excellent dissolution rates. As an added benefit, direct compression can improve the physical and chemical stability of tablets as compared to wet granulation (Bolhuis and Lerk 1973). Direct compression demands the use of excipients with strictly defined properties. Kerry has designed a range of excipients specifically to meet the requirements of the direct compaction process and your needs.

Direct compression is a popular choice because it provides the shortest, most effective and least complex way to produce tablets. The manufacturer can blend an API with the excipient and the lubricant, followed by compression, which makes the product easy to process. No additional processing steps are required. Moisture or heat sensitive ingredients, which
would be contraindicated in wet granulation, can also be used in this type of process. However, it does require a very critical selection of excipients in comparison to granulation processes because the raw materials must demonstrate good flowability and compressibility for successful operation.

Both high and low doses of API present a challenge in this respect. Most APIs tend to have poor compressibility, which affects the quality of tablets if the formulation calls for a large proportion of API. At the same time, there can also be problems when low amounts of actives need to be incorporated into tablets because it is difficult to accurately blend a small amount of active in a large amount of excipient to achieve the desired uniformity and homogeneity. For instance, segregation of the different components can occur. This means there is not a uniform distribution of tablet ingredients being fed to the press, and thus batch to batch consistency of the manufactured tablet cannot be assured.

One of the principal risk factors for segregation is the wide particle size distribution in direct compression formulations, in which active ingredients tend to be at the fine end of the range. Where there is a wide range of particle sizes, there is an increased likelihood of sifting, where the smaller particles 'slip through' the bigger ones. Other bulk powder properties are also important for successful tableting, such as good flowability, and all of these factors combine to place a high requirement on the excipients used for direct compression.

4.4.2 Granulation

Granulation is a process of size enlargement whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified.

Granulation methods can be divided into two types:
1. Wet methods (wet granulation): Use a liquid in the process, binders are added in solution/suspension form

2. Dry methods (dry granulation/slugging): No liquid is used.

If a powder blend's properties do not suit direct compression tableting, manufacturers will turn to granulation processes to create the desired flowability and low dustability. These characteristics are required to minimize tablet weight variations, and ensure high density for high tablet filling weight and high moldability for hard tablet manufacture. Granulation narrows the particle size distribution of a tablet formulation's bulk powder, eliminating segregation problems. This in turn ensures superior compressibility in the tableting process, permitting higher quantities of API to be used and ensuring good active distribution in the tablet. However, granulation is a more time-consuming technique compared with direct compression and there is also a risk of product cross-contamination and product loss during the different processing steps (granulation, drying, sieving). All of these factors can increase costs compared with direct compression.

Dry granulation is more flexible than direct compression. Compared with wet granulation, however, it has a shorter, more cost-effective manufacturing process. Because it does not entail heat or moisture, dry granulation is especially suitable for active ingredients that are sensitive to solvents, or labile to moisture and elevated temperatures. In a suitable formulation a number of different excipients will be needed in addition to the drug. The common types used are diluents, to produce a unit dose weight of suitable size, and disintegrating agents, which are added to aid the break-up of the granule when it reaches a liquid medium, e.g. on ingestion by the patient. Adhesives in the form of a dry powder may also be added, particularly if dry granulation is employed. These ingredients will be mixed before granulation.
4.4.2.1 Dry granulation

The dry granulation process is used to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. In this process the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a ‘slug’) is produced in a heavy-duty tableting press (a process known as ‘slugging’) or the powder is squeezed between two rollers to produce a sheet of material (roller compactor or chilsonator). In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. When a tablet press is used for dry granulation; the powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying degrees of densification. The roller compactor (granulator-compactor) uses an auger-feed system that will consistently deliver powder uniformly between two pressure rollers. The powders are compacted into a ribbon or small pellets between these rollers and milled through a low-shear mill. When the product is compacted properly, then it can be passed through a mill and final blend before tablet compression.

Roller-compaction or dry-granulation equipment offers a wide range of pressures and roll types to attain proper densification. This equipment is loud and dusty compared with other process machinery. Material feed rates are critical for attaining the final objective. The process may require repeated compaction steps to attain the proper granular end point. Typically, a percentage of products Again, successful compaction depend on the compatibility of the products being compressed. If fines are not removed or reprocessed, then the batch may contain too many of them, a situation that
can contribute to capping, laminating, weight, and hardness problems on the tablet press. The need for screening large amounts of fines is common to roller compaction, and the degree to which it can be managed depends on the nature of the ingredients.

4.4.2.2 Wet granulation

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid (the process of adding a liquid solution to powders). The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry. The density of each granule is increased by increasing the amount of binding solution as well as the mechanical action of the mixer. Therefore, controlling the amounts of solution, binder, and mechanical action allows one to control the strength and density of the granule.

Water is commonly used for economic and ecological reasons (safer to nature and operator). Its disadvantages as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat. The primary advantage of water is that it is non-flammable, which means that expensive safety precautions such as the use of flame proof equipment need not be taken. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required. Water mixed into the powders can form bonds between powder particles that are strong enough to lock them together.
However, once the water dries, the powders may fall apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a binder (pharmaceutical glue) is required. Povidone, which is a polyvinyl pyrrolidone (PVP), is one of the most commonly used pharmaceutical binders. PVP is dissolved in water or solvent and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries).

Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules. In the traditional wet granulation method, the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent screening stage breaks agglomerates of granules and removes the fine material, which can then be recycled. Variations of this traditional method depend on the equipment used, but the general principle of initial particle aggregation using a liquid remains in all of the processes. A drying process that is too short will produce granules that have entrapped moisture; if the process is too long, then the granules become very dry and friable. If granules that have been dried only on the outside reach the tablet press, then moisture will escape the granules during compression and cause the granules to stick to the tablet-press tooling, a problem called case hardening. Air flow and temperature control must be uniform.

If the dryer has poor air circulation, then the product on the top will become drier than the product on the bottom. Overly dry product breaks apart easily and is no longer in a granular state. When an overly dry granulation is milled, it produces fine dry particles commonly referred to as fines. Fines do not flow well on a tablet press and thereby cause weight variations. In addition, fines do not compress well and can contribute to capping and lamination, which are common tablet defects. On the other hand, compressing
the lower-tray granulations, which may contain too much moisture, can cause granules to stick to the tablet-press tooling, another situation that produces defective tablets. The error that is most common to granulation processes is the mixing of over dried granules, over wetted granules, and good granules. Once this mixture is on the tablet press, the full range of the previously described problems ensues: capping, lamination, picking, sticking, and tablet weight and hardness variation.

4.5  PRE-FORMULATION

Pre-formulation is a branch of pharmaceutical sciences that utilizes biopharmaceutical principles in the determination of physicochemical properties of a drug substance. The goal of pre-formulation studies is to choose the correct form of the substance, evaluate its physical properties and generate a thorough understanding of the material’s stability under various conditions, leading to the optimal drug delivery system. The pre-formulation study focuses on the physiochemical parameters that could affect the development of efficacious dosage form. These properties may ultimately provide a rationale for formulation design. Also, it will help in minimizing problems in later stages of drug development, reducing drug development costs and decreasing product’s time to market. It gives the information needed to define the nature of the drug substance and provide framework for the drug combination with pharmaceutical excipients in the dosage form.

4.6  NATURAL BINDING AGENTS IN TABLET FORMULATION

Binders are one of the main ingredients required in tablet production. They impart cohesiveness on the powders, thereby improving their flow and compaction properties. Different classes of binders exist in the pharmaceutical industry. Some achieve their effectiveness at high concentrations, while some do so at low concentrations. Povidone and gelatin
have been used over the years at low binder concentrations to formulate good tablets. Currently most researchers concentrate on the use of natural gums at high concentrations to formulate matrix tablets intended for controlled release dosage forms. This is because at such relatively high concentrations, their hydrophilic nature ensures the formation of gels in the presence of water thereby modifying the release characteristics of the incorporated drug (Manuel et al 2000; Sumathi and Ray, 2002). This desire to research mainly on the use of gums to achieve controlled release has led to decline in research on the use of natural gums in the formulation of immediate release tablets, whose formulations are readily undertaken by indigenous manufacturers. Thus, in this study, cashew gum was used at the same concentration range to compare its effectiveness as a binder to those of povidone and gelatin in the formulation of immediate release tablets. Cashew gum is an exudate polysaccharide from Anacardium occidentale tree. The physicochemical properties of the gum have been studied (Cunha et al 2007; Akoto et al 2007). It has similar rheological properties with gum Arabic and has been proposed as a substitute in the paper industry as liquid glue; agglutinant for capsules and pills, as well as polyelectrolyte complex with chitosan for drug delivery in the pharmaceutical industry; and as stabilizer in the food, and cosmetic industries (Akoto et al 2007; De Paula et al 1998).

Binders are agents employed to impart cohesiveness to the granules. This ensures the tablet remains intact after compression. The development of new excipients for potential use as binding agent in tablet formulations continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose. Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability and low cost. Natural binders like different starches, gums, mucilages dried fruits possess binding capacity as well as some other properties like
disintegrant, filler, sustain release, and these natural polymers are much safer and economical than polymers like PVP. Different starches like rice, potato, maize, corn, wheat, tapioca starch and gums like ferula gummosa boiss, gum olibanum, beilschmiedia seed gum, okro gum, aegle marmelod gum, gum cordial, okra gum and cassia roxburghii seeds gum and plant fruit like date palm fruit and orange peel pectin shows good potency as a binding agent.

The role of excipients in determining the quality of a formulation and in many cases the bioavailability of drug from tablets has received considerable attention.Binders are added to tablet formulation to impart plasticity and thus increase the inter-particulate bonding strength within the tablet. The development of new excipients for potential use as binding agent in tablet formulations continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purpose. Binders are agents employed to impart cohesiveness to the granules. This ensures the tablet remains intact after compression as well as improving the flow qualities by the formulation of granules of derived hardness and size. The choice of a suitable binder for a tablet formulation requires extensive knowledge of the relative importance of binder properties for enhancing the strength of the tablet and also of the interactions between the various materials constituting a tablet. To hold various powders together to form a tablet is a binder, fillers usually do not have good binding capacity, binder is either added in dry mix or mix in granulating liquid, binder form matrix with fillers and drug embedded in it, on drying solid binder forms glue which holds the particles together, the wet binder is the most important ingredient in the wet granulation process, most binders are hydrophilic and most times soluble in water.

4.7 TYPES OF BINDERS
Classification on the basis of their application

1. Solution binders are dissolved in a solvent (for example water or alcohol can be used in wet granulation processes). Examples include gelatin, cellulose, cellulose derivatives, polyvinyl pyrrolidone, starch, sucrose and polyethylene glycol.

2. Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples include cellulose, methyl cellulose, polyvinylpyrrolidone, and polyethylene glycol.

Classification on the basis of their source

1. Natural polymers: starch, pregelatinized starch, gelatin, acacia, tragacanth and gumes.

2. Synthetic polymer: PVC, HPMC, methyl cellulose, ethyl cellulose, PEG.


4.8 NATURAL POLYMERS

4.8.1 Advantages of Natural binder

- Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability and low cost.
They can also be used to modify the release of drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug.

They act as vehicles which transport the incorporated drug to the site of absorption and are expected to guarantee the stability of the incorporated drug, the precision and accuracy of the dosage, and also improve the organoleptic properties of the drugs where necessary in order to enhance patient adherence.

They should optimize the performances of dosage forms during manufacturing as well as when patients ingest them.

4.8.2 Disadvantage of Polymer Binders

Polymer binders can lead to processing difficulties such as rapid over granulation. Over time they occasionally lead to tablet hardening and a decrease in dissolution performance.

When polymer binders are chosen, the addition of strong disintegrants such as super disintegrants is typically required but these are considerably expensive and have a negative effect on product stability as well as film coating appearance of the finished products.

4.9 STARCH AS BINDER

There are various types of natural polymers like starch, gums, pregelatinised starches are used as binding agent. Starches like rice starch, maize starch, potato starch, wheat starch, corn starch are well known for their
binding and disintegrating properties but some other starches like enset starch and banana starch can also be used as binding agent. Starch is also used as fillers. Starch is widely used as thickening, stabilizing, gelling and/or filling agent in many food applications and it considered as the most used excipient in pharmaceutical formulations. It has many pharmaceutical applications and it is used mainly in tablets as filler, binder or disintegrant. Starch is the major carbohydrate reserve in plant tubers and seed endosperm where it is found as granules. It contains mainly two types of polymer molecules; several million of highly branched amyllopectin molecules (normally 70-80%) accompanied by a higher number of largely linear amylase molecules (normally 20-30%).

Starch is one of the most widely used excipients in the manufacture of solid dosage forms. Starches from different sources have been evaluated and used as excellent binders in either mucilage or the dry powdered form. Although maize starch is the most frequently used excipient in tableting, researchers have tried to develop botanical starches for use tablet excipients. The use of Dioscorea rotundata as a binder and disintegrant in tablet formulation and Itiola also investigated the compressional properties of this particular starch. The effects of pigeon pea and plantain starches on the compressional, mechanical and disintegration properties of Paracetamol tablets have been investigated. The role of ginger starch as binder in acetaminophen tablets was found.

### 4.9.1 Starch 1500 as a Binding Agent

Starch 1500 performed as an excellent binder producing a granulation that was compressible and produced Lamivudine tablets of improved hardness and friability compared with those prepared with povidone. The formulation of Lamivudine tablets with Starch 1500 exceeded the disintegration and dissolution performance of the povidone formulation that utilized a super disintegrant. The nature and amount of the binders were
found to alter the disintegration and dissolution rates of the tablets by reducing their wet ability as measured by the adhesion tension of water. During pharmaceutical granulation, the objective is to produce granules that have a uniform (and repeatable) distribution of drug particles within the bulk carrier (excipient) solid. This can be difficult to achieve and both drug depletion and enrichment in granules can occur. A linear relationship has been found to exist between the adhesion of water on the tablets and their disintegration and dissolution rates.

4.9.2 Tapioca Starch as a Binding Agent

The use of a natural product tapioca starch as binding agent in the formulation of Diclofenac tablets was identified. The nature and amount of the binders were found to alter the disintegration and dissolution rates of the tablets by reducing their wet ability as measured by the adhesion tension of water. During pharmaceutical granulation, the objective is to produce granules that have a uniform (and repeatable) distribution of drug particles within the bulk carrier (excipient) solid. This can be difficult to achieve and both drug depletion and enrichment in granules can occur. A linear relationship has been found to exist between the adhesion of water on the tablets and their disintegration and dissolution rates.

The starch was extracted from root tubers of cassava (Manihot esculenta) according to the method of Alebiowu using established procedures. Cassava tubers were peeled, washed and cut to small pieces. These small pieces were then soaked in distilled water for specified period of time i.e. for 1 h. At the end of the steeping period, the softened tubers were milled to a pulp, and more distilled water was added to give dilute slurry which was sieved using mesh size 100.
4.9.3 Ginger Starch as a Binding Agent

Rhizomes of ginger purchased from a local market in Nsukka were washed with water, peeled, weighed, reduced to smaller pieces and properly ground using an electric grinder. Enough quantity of water was added to soak the material for 5 h and sieved with a clean muslin cloth. The ground mass was thoroughly washed with water onto the muslin cloth into a collecting vessel to release the starch granules embedded in the parenchyma cells. The content of the collecting vessel was then allowed to settle for 2 h and the yellowish supernatant was decanted. The whitish starch mixture was stirred with addition of water and allowed to stay for 2 h and the supernatant decanted. Series of redispersions and decanting were done to remove impurities. The settled starch was scrapped off and placed into white paper to dry in open air. The starch as then milled and weighed.

4.9.4 Rice Starch as a Binding Agent

Starch isolation by neutral protease used rice flour (100g) mixed with deionized water (200 mL) in a 500-mL reaction beaker. The temperature was maintained at 50°C with a circulator, and the slurry pH was adjusted to 7.0 with 1.0 N NaOH. Different levels of neutral protease (0.01, 0.03, or 0.05% on rice flour basis) were added to the slurry and reacted for 1, 3, or 5 hr with constant stirring using a magnetic stirrer. The flour slurry was then blended with a Waring blender at a high speed for 2 min after the protease digestion. The slurry was passed through a 63-m screen and centrifuged at 1400×g for 10 min. The starch layer was reslurried and washed with deionized water 3 times. The isolated starch was dried at 45°C for 48 hr.
4.9.5  Corn Starch as a Binding Agent

**Stage 1** entailed of crushing the dry kernels with a hammer, removing the seed coat, separating the germs, and collecting the starch without drying it under the fan.

**Stage 2** is briefly described in three steps

- Three corn kernels were placed in screw-top 25-ml test tubes. Sodium meta-bisulfite 0.45% (2 ml) were added to each tube before incubation in a 50°C water bath for 48 hr (± 2 hr) to soften the kernel, enhance peeling of the seed coat, and preserve the kernel during steeping.

- After incubation, the sodium metabisulfite was decanted and the seed coat and germ were manually removed from the kernels. A mortar and pestle was used to grind endosperm as fine as possible.

- The resulting starch was dried in front of fan overnight.

4.9.6  Potato Starch as a Binding Agent

Enzyme solution was prepared by mixing thoroughly 1g of the enzyme in 10ml of distilled water by a glass rod in a 20ml test tube. The potatoes were washed under tap water so that any dirt adhered to it may be removed. After washing the potatoes were cut into small pieces without peeling with a stainless steel knife to facilitate grinding. Grinding was done in Commercial grinder having motor rpm of 15000 for 1 min and 15 s after standardizing the time. The ground potato meal was then transferred to a 500 ml conical flask and appropriate amount of water was added to the meal. The prepared enzyme solution was added to the potato meal using a pipette.
For concentration of 0.1g per 100g of potato meal, 1ml of the enzyme solution was added to 100g of potato meal. The flask was cotton plugged and kept in incubator cum shaker at 45°C with a shaking speed of 125 rpm. The pH of all the samples varied between 6 and 7 and cellulase enzyme is effective between pH 3 and 7. So, the natural pH of the broth was not changed. After incubation the resultant slurry was screened by a nylon tea strainer of mesh size of 100 into a 400 ml beaker. During screening the pomace was washed two times in 150 ml of tap water. Sedimentation was done for 1 h to separate the starch from the other components of the filtrate containing starch.

4.9.7 Wheat Starch as a Binding Agent

Starch was isolated from flour using a modified protein digestion procedure from wheat flour (12.1% protein; 13.0% moisture content). Flour (0.3 g) was placed in 50-mL plastic centrifuge tubes with 5.0 mL of water and 2 mL of 0.8% pepsin A (P7012, Sigma, St. Louis, MO) in 0.04N HCl and incubated for 60 min at 37°C. After protease treatment, 1.0 mL of 0.08% Hemicellulase 90 (90,000 U/g activities, a gift from Amano Enzyme U.S.A., Lombard, IL) in 0.1M sodium acetate buffer (pH 4.5) was added to the mixture and incubated for 3 hr at 45°C. A detergent mix (1 mL) (5% SDS, 5% Triton X-100, 5% Tween 40, and 5% Triton X-15) was added after incubation, and the suspension was vortex-mixed for 30 sec. The enzymetreated starch was centrifuged at 2,500 rpm for 5 min in a Sorval SS-34 rotor and SS-3 centrifuge. The starch was washed twice with water; the supernatant was discarded and the starch pellet was re-suspended in 5 mL of water followed by vortex mixing for 30 sec and centrifuging at 2,500 rpm for 5 min. A final water wash was conducted in a micro centrifuge tube with 1.0 mL of water and centrifuged for 1 min.
4.10 NATURAL GUMS AS BINDER

The development of new excipients for potential use as binding agent in tablet formulations continues to be of interest. This is because different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purposes. In recent times, increasing attention has been given to the application of gums of various sources as pharmaceutical excipients. Gums generally are polysaccharides which are polymeric in nature of natural substances obtained from woody and non-woody plant parts such as bark, seeds, sap, roots, rhizomes, fruits and leaves. Plant gums are widely used in diverse applications for the formulation of pharmaceutical dosage forms. The major application of gums is in tablets as binding agent.

4.10.1 Ferula Gummosa Boiss as Binding Agent

Ferula gummosa Boiss is one of the natural plants of Iran. The whole plant, but especially the root, contains the gum resin igalbanumi. Enauyatifard et al studied the comparative effects of galbanum gum and two standard binding agents, polyvinylpyrrolidone and acacia, on characteristics of acetaminophen and calcium carbonate compacts. The Ferula gummosa gum was extracted and its swelling index was determined. Acetaminophen and calcium carbonate granules were prepared using the wet granulation method and were evaluated for their micrometrics and flow properties, while the compacts were evaluated for mechanical properties using the hardness, tensile strength, and friability. The drug release from acetaminophen compacts was assessed using dissolution studies.

Ferula gummosa Boiss (Apiaceae) is a perennial plant native to central Asia, growing in the northern and western parts of Iran. The whole plant, but especially the root, contains the gum resin igalbanumi. Several
medicinal actions such as anticonvulsant, expectorant, antispasmodic and anticitardarrah have been reported for F. gummosa plant and its gum. Externally, it is used as a plaster for inflammatory swelling, ulcers, boils, wounds and skin complaints. Numbers of schizogenous ducts of F. gummosa are in the cortex containing the resinous gum.

4.10.2 Gum Olibanum as Binding Agent

The binding properties of mucilage extracted from Gum Olibanum. The main objective is to exploit the use of Gum Olibanum as natural binding agent in development of oral tablet formulations taking Fruosemide as model drug. Some of the mucilage has also been used in tablet formulations as binding agent also to sustain the drug release. Natural mucilage are nontoxic, non-irritant and act as stabilizers, emollients and stiffening agents. Gum Olibanum mucilage was evaluated for its granulating and binding properties in tablets, using furosemide as a model drug. Mucilage was used in different concentrations of 5.7 and 10 % w/v. The granules were prepared by wet granulation technique (Awen et al 2010).

4.10.3 Beilschmiedia Seed Gum as Tablet Binder

The Beilschmiedia gum was isolated from the edible seeds of Beilschmiedia mannii (family Lauraceae) and evaluated for its binding properties at a concentration range of 0.5- 10 % w/w in paracetamol tablets with official gelatin as a control. A comparative analysis was conducted that shows the granules bound with Beilschmiedia gum were relatively bigger and harder than the ones obtained with gelatin gum. The hardness, disintegration time and dissolution rate increased with increase in concentration of Beilschmiedia gum. Tablets containing 5 % w/w of Beilschmiedia gum had a binding capacity approximately twice that of gelatin with a dissolution rate of
91% after 30 min. They concluded that Beilschmiedia gum possesses potential as a commercial binding agent.

4.10.4 Okro Gum as Tablet Binder

The okro gum is suitable as a binder for pharmaceutical tablet formulations. A comparative evaluation of Abelmoschus esculentus (okro) gum as a binder in the formulation of thiamine hydrochloride granules and tablets was performed. Gelatin, acacia and polyvinylpyrrolidone (PVP), were employed as standard binders for comparison. The properties of granules and tablets evaluated were; flow rate, angle of repose, density, weight uniformity, hardness, friability, disintegration time and dissolution rate. The granules had good flow properties. However, binder concentration influenced flow characteristics. Okro gum gave the highest hardness/friability ratios. It also prolonged disintegration time and dissolution time and dissolution rate. Hence, okro gum may not be useful as a binder in conventional tablet formulation. But the okro gum could be a good candidate for evaluation as a binder or hydrophilic polymer in sustained release tablet formulation.

4.10.5 Okra Gum as a Tablet Binder

The aim is to evaluate the effectiveness of a new binder extracted from Hibiscus esculentus (Okra gum) in tableting. Okra gum was extracted from the pods of Okra fruit by maceration in distilled water followed by filtration of viscous solution as well as precipitation of gum extract by using acetone. To evaluate the binder effectiveness, two models, including a placebo formulation (lactose) and a drug formulation (Acetaminophen, Ibuprofen, and/or Calcium acetate) were evaluated. Granules were prepared by different concentrations (0.5-6 %w/w) of Okra gum and tableted using a Kilian single punch press. Cornstarch (12.5 % w/w) and P.V.P (22 %w/w) were employed as the standard binders for comparison.
4.10.6 Cashew Gum as a Tablet Binder

Cashew gum is the exudate from the stem bark of Anacardium occidentale Linn (family, Anarcardiaceae). The plant is native to Brazil and grows in many tropical and sub-tropical countries. In Ghana, the plant is found mostly in cashew growing areas such as Sampa, Wenchi, Bole, Jirapa and Ejura where they are commercially cultivated for the utilization of the nuts. Gums from cashew plants from various parts of Ghana are reported to possess the following physicochemical characteristics,

- Moisture content (9.8 – 13.2 %)
- Insoluble matter (1.9 – 4.8 %)
- Total ash (0.5 – 1.2 %)
- Protein content (1.27 – 1.80 %)
- Total sugars (0.96 – 2.10 mg/g)
- Total phenols (0.21 – 2.26 %)

Cashew gum is chemically composed of 61 % galactose, 14 % arabinose, 7 % rhamnose, 8 % glucose, 5 % glucuronic acid and < 2 % other sugar residues while hydrolysis of the gum yields L-arabinose, L-rhamnose, D-galactose and glucuronic acid. Cashew gum has been studied widely for various pharmaceutical applications as it is inexpensive, non-toxic, biodegradable, and possesses appropriate physicochemical characteristics. As cashew gum shares similar characteristics as gum Arabic, it has been suggested for use as an agglutinant for capsule and pills in place of gum Arabic in the pharmaceutical and cosmetic industries.

Cashew gum modified by carboxymethylation with monochloroacetic acid as etherifying agent was used to form polyelectrolyte complexes with chitosan for possible use in controlled drug delivery. The
gum was employed as a binder in lactose-based tablet formulations containing tartrazine dye where the tablets produced were shown to exhibit good hardness and friability properties. Cashew gum has also recently been utilized as a binder in paracetamol tablet formulations where the gum imparted better mechanical properties to the tablets than povidone or gelatin. The gum has been evaluated as a gelling agent in an aceclofenac topical gel formulation where the gel containing 5 % w/w cashew tree gum was found to be suitable for topical application based on its physicochemical properties.

There are large numbers of natural polymers have been used in pharmaceutical preparations. Natural substances like starches, mucilages, gums and also dried fruits can be used as binding agent. They have been shown good potential as binding agent as well as they possess some other properties like disintegrating agent, fillers, sustain releasing agent. Natural polymers shown good binding property in wet granulation, granules are stable and less friable in comparison with other binders. They can also be used to modify the release of drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug. Furthermore, they act as vehicles which transport the incorporated drug to the site of absorption and are expected to guarantee the stability of the incorporated drug, the precision and accuracy of the dosage, and also improve on the organoleptic properties of the drugs where necessary in order to enhance patient adherence. They should optimize the performances of dosage forms during manufacturing as well as when patients ingest them.

4.11 BINDERS AS STRENGTH-ENHANCING MATERIALS IN PHARMACEUTICAL TABLETS

A binder is a material that is added to a formulation in order to improve the mechanical strength of a tablet. In direct compression, it is
generally considered that a binder should have a high compactibility to ensure the mechanical strength of the tablet mixture. Alternatively, amorphous binders which undergo pronounced plastic deformation have been suggested to provide an effective means of creating a large surface area available for bonding (Nystrom et al 1993). However, the mechanisms behind the strength enhancing effect of a binder are not yet fully understood. The rational choice of suitable binder in a formulation requires extensive knowledge of which properties of a binder are important for the strength enhancing effect. Only then would it be possible to predict the function of a binder in a formulation. Increased knowledge of the functionality of a binder would enable a more rational approach to tablet formulation. Furthermore, the extensive use of powder mixtures renders knowledge of how different materials interact with each other important. The development of direct compression as an alternative method to wet granulation has stimulated efforts to modify and improve the binders used in direct compression (commonly referred to as filler-binders) (Shangraw 1986; Bolhuis and Chowhan 1996; Armstrong 1997). The role of the binders in direct compression is especially important when a high dose of a poorly compressible drug is included in the formulation.

4.12 DISTRIBUTION OF BINDERS - COMPARISON BETWEEN DIRECT COMPRESSION AND WET GRANULATION

In direct compression, the binder is added in its dry state, whereas a liquid is employed in wet granulation. Besides the common aim of enhancing the bonding properties between particles or granules, the binder in wet granulation also aims at improving the binding between powder particles during agglomeration. Addition of a binder in its liquid state would probably facilitate its distribution; it can be more difficult to obtain homogeneous distribution with a dry binder. Therefore, binders added as dry powders are
generally less effective than when added as solutions (Nyström et al 1982). The binders used in wet granulation are generally polymeric materials, which are amorphous or semi-crystalline, e.g. polyvinylpyrrolidone and gelatin. These binders are considered plastically deformable, which is probably an important attribute for their effective distribution. In direct compression, however, focus has mainly been on using a binder with a high compactibility.

4.13 EFFECT OF BINDERS ON MECHANICAL STRENGTH OF DIRECTLY COMPRESSED TABLETS

The addition of a binder to a compound has been suggested to change the surface properties of the coarse compound particles as they are covered by the small binder particles. It was proposed that this surface coverage increased the surface area available for inter-particulate bonding, thus increasing the number of bonds and also possibly creating stronger bonds, with a subsequently increased mechanical strength (Nyström et al 1982; Duberg and Nyström 1985; Nyström and Glazer 1985). Addition of a binder which increases elasticity can decrease tablet strength because of the breakage of bonds as the compaction pressure is released (Nyström et al 1982). The addition of second component, such as a binder, to a compound has also been reported to affect and modify the volume reduction behavior of the compound (Wells and Langridge, 1981; Yu et al 1989; Larhrib and Wells, 1998). However, others have observed that volume reduction of the materials constituting as binary mixture occurred independently of each other (Humbert-Droz et al 1983). In a binary mixture consisting of components A and B, three types of bonds may occur after compaction: A-A, A-B and B-B. The relative importance of these bonds was used to explain the behavior of a binary mixture (Leuenberger 1982). A quantitative expression based on compressibility and compactibility parameters of pure materials has been used to estimate and predict the behavior of mixtures (Leuenberger, 1982; Jetzer,
1986). Jetzer (1986) concluded that the compaction characteristics of mixtures were principally governed by the behavior of the individual materials and that interactions were most likely to occur with mixtures of components with dissimilar compaction mechanisms.

4.14 ECONOMIC NATURAL BINDERS

4.14.1 Okra Gum - An Economic Choice for Capping and Lamination in Tablets

Paracetamol tablets are the most consumed analgesic and antipyretic tablets in Nigeria. For this reason, majority of the indigenous pharmaceutical manufacturers produce paracetamol tablets. The ingredients relevant to the production exercise are virtually imported. Although there are many sources of pharmaceutical raw materials in Nigeria, the drawback has always been the inability of the local industries to generate pharmaceutical grade products due to production costs, and some toxicological studies required by regulatory authorities. However, okra pods which are a potential source of pharmaceutical raw material(s) in Nigeria, whose production costs low, and which may not require toxicological studies since they are eaten either raw or cooked by Nigerians, yield a suitable gum that is useable as safe pharmaceutical raw material; but has been neglected over the years. Okra pods are fruits of the plant *Abelmoschus esculentus* L.moench, family Malvaceae.

In Nigeria okra is grown basically in all states of the federation both as rain fed and irrigated crops. In the peak season, it is produced in large quantities much more than what the local populace can consume, thus leading to heavy wastages. Okra gum, which is a natural polymer, has advantage over synthetic and semi-synthetic polymers, in that it is cheap and easily available, non-irritant, biodegradable, biocompatible, and eco-friendly. Okra gum has
been investigated as a binding agent in tablet dosage forms, and has been shown to produce tablets with good hardness, friability and drug release profiles. It has also been utilized as a plasma expander. The indigenous pharmaceutical manufacturers should therefore exploit this economic source of excellent pharmaceutical excipient that has been studied. Paracetamol powder is an elastic material, and therefore needs a good binder for its formulation into tablets in order to forestall the incidence of capping and lamination (the major problems encountered by paracetamol tablet manufacturers).

Some manufacturers have employed various binders, for example, povidone (PVP), corn starch, acacia, hydroxypropylmethyl cellulose (HPMC) either alone or in-combination with other binder(s) in the formulation of paracetamol tablets. Measurable mechanical properties of tablets include: tensile strength, packing fraction, friability, disintegration time and bonding index, strain index, etc. In conventional tablets binders' have excellent ability to hold powder particles, but the bonding index is does not give sufficient guarantee to that capping and lamination. It is very annoying problems in tablet production. It is this realization that informed the introduction of brittle fracture index (BFI) by Hiestand and his colleagues in 1977 to estimate the ability of materials to ameliorate capping and lamination in tablets. Bond strength and lamination tendencies are two important mechanical properties of tablets that are measurable by tensile strength (TS) and brittle fracture index (BFI) value respectively. All literature search on the binding property of okra gum showed that no researcher has worked on estimating the ability of the gum to forestall the incidence of capping and lamination in tablets. It is based on this and the quest to explore local economic alternatives for excellent binders that this research was designed. In this study therefore, the mechanical and dissolution properties of paracetamol tablets formulated with
Okra gum as binder are compared with those of paracetamol tablets formulated with PVP, gelatin, or HPMC as binder.

**Okra Gum**

Okra gum is a natural polysaccharide composed of d-galactose, L-rhamnose and L-galacturonic acid (Agarwal 2001). It is soluble in cold water and used in the food industry as an emulsifying and foam-stabilizing agent (Agarwal 2001). Okra gum is appropriately comparable with standard binders. Okra gum at concentrations of 1 and 2 % (w/w) could produce suitable lactose granules. Therefore, concentration of 3% for Okra gum was chosen as the optimum level to produce granules. However, based on our preliminary studies (data was not shown) the 5% concentration of binder was preferred for granulation of the poor compressible (Acetaminophen) and high dosage (Ibuprofen) drugs.

An increase in binder concentration increased the hardness and disintegration time and decreased friability values of the tablets. Okra gum as a binder produces some tablet formulations with good hardness, friability, and disintegration time and dissolution rate. The type and amount of binders decisively influence the characteristics of tablets prepared by wet granulation procedure. Commonly used binders like acacia, gelatin, starch and hydrolyzed starch have natural origin. The aim of this study was to evaluate the effectiveness of a new binder extracted from Hibiscus esculentus (Okra gum) in tableting. Okra gum was extracted from the pods of Okra fruit by maceration in distilled water followed by filtration of viscous solution as well as precipitation of gum extract by using acetone. The physical properties of granulates and those of the tablets including disintegration time and dissolution rate were studied. The properties of placebo granulate (bulk and tapped density, granule strength, flowability) as well as those of tablets (hardness, friability, and disintegration time) were generally good. However,
this binder prolongs the dissolution rate of some slightly soluble drugs and hence may be good candidate for sustained release formulations. The mechanical properties of paracetamol tablets formulated with okra gum as binder at the concentrations used are similar to those of povidone, gelatin, and HPMC. Okra gum is superior to the three binders in its ability to reduce brittle fracture tendency in paracetamol tablets. And because it can achieve very good drug release profile and mechanical properties at low binder concentration range (1.0%w/w – 2.0%w/w) it should be better explored and exploited as an alternative to povidone in tablet formulation since its production would generally be cheaper; thus invariably leading to lower cost of tablet production.

Thus it is recommended that okra gum be employed in the formulation of conventional tablets at concentration range of 1.0 – 2.0%w/w since beyond this range, reduction in BFI is not appreciable, and drug release may not compare favorably with povidone. Furthermore, as okra gum is cheaper and easier to source, and a much smaller amount is necessary in conventional tablet formulation, it is strongly recommended also that our indigenous manufacturers should invest in its exploration and exploitation.

4.14.2 Classification, Grouping and Ranking of Binders in Tablet Formulation by Brittle Fraction Index (BFI) Tool

A well formulated tablet possesses some essential properties which include its robustness in order to withstand post compaction handling and transportation (Rubinstein 1990). The production of tablets is a complex multistage process that demands sound knowledge and experience in the art. Tablets are solid dosage preparations each containing a single dose of one or more active substances and are usually obtained by compressing uniform volumes of particles (BP, 2003). Oral tablets have remained the most common dosage form by which medicaments are usually administered to patients
because of their advantages over the other dosage forms (Mattson 2000; Armstrong 2002; Nachaegari and Bansal 2004). The most common problem during the production include: binding, sticking, picking, filming, chipping, cracking, capping and lamination (Bandelin 1989).

**Capping and lamination**

Capping and lamination are very embarrassing problems in tablet production, packaging, transportation and dispensing. A tablet is said to have capped when the upper or lower segment of the tablet separates horizontally, either partially or completely from the main body of the tablet and comes off as a cap during ejection from the tablet press or during subsequent handling. Capping is usually caused by air entrapment in a tablet during compaction and subsequent expansion of the tablet on ejection from the die. Its other causes include presence of large amount of fines in the granulation, use of granules that have very low moisture content, insufficient amount or improper binder, high plastoelasticity of the tableting base, excessive compression force, and lack of sufficient clearance between the punch and the die wall (Okor 2005).

Lamination on the other hand means the separation of a tablet into two or more distinct horizontal layers, and its causes are similar to those of capping. In order to forestall tableting problems, preformulation studies are usually conducted to select suitable excipients for the production of specific active pharmaceutical ingredients (APIs). Binders act to ameliorate capping and lamination by decreasing the plastoelasticity of pharmaceutical powders. Materials used as binders predominantly display plastic compaction characteristics, and when incorporated into elastic or brittle powders there is resultant increase their plasticity and conversely reduction in their plastoelasticity. Plastoelasticity refers to the relative elastic to the plastic compression property of a pharmaceutical powder (Uhumwangho and Okor 2004). BFI has been used as a measure of plastoelasticity of pharmaceutical
powders (Ejiofor et al 1986; Esezobo and Pilpel 1987; Okor et al 1998; Eichie and Okor 2002; Onyekweli et al 2004) and also to estimate the tendency of a tablet to cap or laminate under a diametric stress (Hiestand et al 1977; Alebiowu and Itiola 2002; Iwuagwu and Onyekweli 2003; Eichie et al 2005). BFI is measured by comparing the tensile strength (To) of a tablet with Centre hole to the tensile strength (T) of a similar tablet without a Centre hole. The Centre hole is a built-in model defect, which simulates the actual voids formed in the tablets (due to air entrapment) during manufacture. The ability of a material to relieve stress around the voids by plastic deformation is the property estimated with BFI (Williams III and McGinity 1988). BFI is calculated with the equation (Hiestand et al 1977). BFI values range from 0 to 1. A high value (tending to 1) implies high fracture tendency, while a low value (tending to 0) implies low fracture tendency. Tablet formulations with BFI values \( \geq 0.5 \) are prone to high fracture tendencies (Hiestand et al 1977).

Many pharmaceutical powders have poor compaction properties and are prone to extensive capping and lamination after production especially if inadequate or improper binder is used in their formulation. Incorporation of adequate amounts of proper binders to pharmaceutical powders reduces the BFI values of their compacts and therefore ameliorates capping and lamination tendencies. Materials used as binders in tablet production have been classified based on nature or origin (Lund 1994; Ofuer III and Klech-Gelotte 2002). This work aims at utilizing paracetamol, a drug with high capping and lamination tendency as a model to study the possibility of employing BFI as a tool in the classification, grouping and ranking of binders in tablet formulation. The moisture contents of the granules did not differ appreciably and therefore might not have contributed significantly to their dynamic and compaction properties. It was noted during the experiment that the granules had small amount of fines and this resulted to moderate tapped
volume reductions and consequently moderate flow characteristics, which however may be improved by glidant incorporation.

The steeper slopes of plant gums, PVP, gelatin and HPMC, are indications of their greater effectiveness in BFI reductions than starches and CMC. By this, the binders were grouped as and it is evident that no particular class of binders occupied a unique group within the range of BFI values realized in this study. Rather, binders from various classes at different/similar concentrations appear within each range. This grouping is very significant in formulation development in that it may serve as a guide for scientists to narrow their search for appropriate binders and suitable concentrations to be applied in formulating not only paracetamol but also other elastic natured powders into tablets with highly reduced tendencies to fracture. Furthermore, within each group, binders possess dissimilar abilities in the reduction of BFI; hence they can be ranked based on their effectiveness. From this ranking, it is evident that from an array of binders that can impart the same range of BFI value at the same concentration, choice may still be made based on the level of effectiveness of each binder.

However, it must be stressed that this choice should also be guided by the dissolution profile desired from the formulation. This resulted from the added disintegrant effect that starches have been established to manifest when they are incorporated as pastes during granulation (Rudnic and Schwartz, 2000). The amount of drug released in 15min was used as a discriminating test to judge the release profile of tablets. It is evident from this study the brittle fracture index is a useful tool for the grouping of binders based on their abilities to ameliorate capping and lamination in tablets. Its usefulness also extends to the ranking of binders based on their levels of effectiveness in solving the problem of capping and lamination. However, ‘families’ of binders based on nature or origin could not be classified using BFI since no
‘family’ occupied a unique range of BFI values within the concentration ranges used in the present study.

4.14.3 Cashew Gum - An Economic Choice of Natural Binder

Cashew Gum

The cashew is native to northeast Brazil. The leaf of the cashew tree contains compounds that are toxic to other plants and animals. The trees produce nuts, fruits, gum, and charcoal. The only cashew product traded in any quantity internationally, however, is the nuts. The cashew fruit is as unusual as the rest of the tree. Several products can be produced from the cashew tree. These include nuts, fruits, nutshell liquid, and resin to name but a few. Of all these products only cashew nuts have significant trade internationally. The cashew fruit (cashew apple) is rich in vitamins and amino acids. It can be used for making many typical fruit products such as jellies, jams, juice, wine, and liquor. Cashew gum is an exudate polysaccharide from Anacardium occidentale tree. The physicochemical properties of the gum have been studied (Cunha et al 2007; Akoto et al 2007). It has similar rheological properties with gum Arabic and has been proposed as a substitute in the paper industry as liquid glue; agglutinant for capsules and pills, as well as polyelectrolyte complex with chitosan for drug delivery in the pharmaceutical industry; and as stabilizer in the food, and cosmetic industries (Akoto et al 2007; De Paula et al 1998).

Cashew nutshell liquid is a natural resin that is extracted from the honeycomb structure of the cashew nutshell. It contains 90 percent anacardic acid and 10 percent cardol. Both are caustic and can contaminate the nuts and blister the skin of the shellers (Davis 1999). The liquid is a by-product of the cashew industry and a versatile industrial raw material. There is considerable potential for its utilization in the development of drugs, antioxidants,
fungicides, and other chemicals. In the tropics, the liquid from cashew shells is used in some medicines for the treatment of ailments such as scurvy, warts, ringworm, cancerous ulcers, and even elephantiasis. The oil is also used for treating timbers to make them termite proof. The major use is to make cashew friction particles for the brake lining industry. The liquid is also used to make resins, varnishes, paints, plastics, insecticides, preservatives, drying oil and epoxy, binders in automotive strip linings and brake linings, and heavy duty coatings that have the ability to stick to poorly prepared surfaces. Cashews are easy and inexpensive to produce.

Disintegration times were longest for GEL formulated tablets and least for PVP formulated ones. At binder concentrations of 1.0 – 3.0% (w/w) Cashew Gum (CAG) released the highest cumulative amount of drug in 30 min; from 4.0 – 5.0% (w/w) cumulative amount released became highest for PVP formulated tablets. GEL formulated tablets generally released the least amount. CAG gum therefore having imparted better BFI than PVP or GEL, and does not hinder drug release is strongly recommended as an alternative to the more expensive PVP or GEL for immediate release tablet formulations. Thus, in this study, cashew gum was used at the same concentration range to compare its effectiveness as a binder to those of povidone and gelatin in the formulation of immediate release tablets.

Tablets formulated with Cashew gum had the lowest tensile strengths, although the differences between their values and those of tablets formulated with povidone, or gelatin were not appreciable. Tablets brittle fracture indices displayed inverse relationship to binder concentration. Since BFI is an inverse measure of localized stress relief, it implies that the ability of the binders to reduce the tendency of paracetamol tablets to cap or laminate increased as binder concentration in granules increased. This they achieved by imparting plasticity on otherwise elastic natured paracetamol powder. It
therefore implies that the lower the BFI value imparted by the binder, the higher is the binder’s ability to prevent capping and lamination in tablets. Thus, cashew gum which produced tablets with the lowest BFI would relief localized stress in tablets better than povidone or gelatin. On friability, the tablets with cashew gum yielding tablets of lower friability than povidone up to binder concentration of 3.0% (w/w).

Tablets formulated with povidone displayed gradual increase in disintegration time with increase in binder concentration unlike those formulated with gelatin or cashew gum. However tablets formulated with cashew gum had shorter disintegration time than those formulated with gelatin. Table 2 shows the cumulative percent of paracetamol released by all tablet formulations over 30 min intervals. Tablets formulated with povidone generally released the highest amount of drug from 5 to 25 min interval. But the cumulative amount of drug released in 30 min was highest with tablets formulated with cashew gum at binder concentration range of 1.0-3.0% (w/w). Beyond 3.0% (w/w) binder concentration, tablets formulated with povidone had the highest release over those formulated with cashew gum or gelatin. This implies that granules resulting from the disintegration of tablets formulated with povidone disintegrated faster into fine particles thereby enhancing the dissolution of paracetamol particles.

The amounts of drug released by tablets formulated with cashew gum were close to those of tablets formulated with gelatin at concentration of 5.0% (w/w) (which is actually not satisfactory for immediate release tablets). Thus it is recommendable that the use of cashew gum in the formulation of immediate release tablets should be limited to 1.0-3.0% w/w concentration range in order to achieve good mechanical and release properties. The mechanical properties of paracetamol tablets formulated with cashew gum as binder at the concentrations used are similar to those of povidone and gelatin.
Cashew gum is superior to both binders in its ability to reduce brittle fracture tendency in paracetamol tablets. And because it can achieve very good release profile and mechanical properties at low binder concentration range (1.0-3.0%, w/w) it should be better explored and exploited as an alternative to povidone and gelatin in tablet formulation since its production would generally be cheaper; thus invariably leading to lower cost of tablet production.