EVALUATION OF LOCAL GUM OF *ACACIA POLYACANTHA* AS A BINDER IN TABLET FORMULATIONS

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By

TEGEGNE AKLILU (B.Sc.)

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DEDICATED TO FAMILY
ESPECIALLY MY MOTHER
WHO HAS BEEN THERE FOR ME,
ALL THE TIME

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ACRONYMS

BFI: Brittle Fracture Index

BP: The British Pharmacopoeia

CMC: Carboxymethylcellulose

EC: Ethylcellulose

HCl: Hydrochloric acid

HMC: Hydroxymethyl cellulose

HPC: Hydroxypropyl cellulose

HPMC: Hydroxypropylmethyl cellulose

MC: Methylcellulose

MCC: Microcrystallinecellulose

PEG: Polyethylene Glycol

PVP: Polyvinylpyrrolidone; Povidone, Kollidon®

PVP K30: Polyvinylpyrrolidone, Kollidon® of grade 30000

T_{50}: The time taken for 50% of the drug to be released in the dissolution

TS: Test Solution

USP: The United States Pharmacopoeia

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ABSTRACT

Acacia gums are dried gummy exudates obtained from the stems and branches of acaica spp. (fam. Leguminosae). *A. senegal* is the source of most gum arabic of international trade and it finds wide applications in pharmaceutical, food and cosmetic industries. Other African acacia species of economic importance include *A. seyal, A. drepanolobium* and *A. polyacantha*. In this study, a local gum of *A. polyacantha* was evaluated as a tablet binder. Paracetamol and chloroquine phosphate were used as model drugs. The physico-chemical properties of the purified gum, and its rheological properties were investigated. The gum was found to have similar properties to Acacia BP (odourless, white to yellowish brown, glassy, no tannins, no starch or dextrin present and moisture content of 11.6%). It exhibited Newtonian flow up to 40% w/v solution but less viscosity than Acacia BP. Granules prepared with different concentrations (5 - 30% w/v for paracetamol and 5-20% w/v for chloroquine phosphate) of the gum mucilage were characterised for particle size distribution, bulk, tapped and true densities, friability and flow properties. The granules were mixed with Ac-Di-Sol® (4%) and magnesium stearate (0.5%) and compressed into tablets at different compression forces. The optimum binder concentration (X_1) and compression force (X_2) (independent variables) of both substances (paracetamol and chloroquine phosphate) were investigated using 2^2 factorial design taking crushing strength (H), disintegration (DT) and friability (Fr) as response variables. Polynomial equations were generated for the responses ($H = 84.175 + 26.825X_1 + 33.375X_2 + 5.625X_1X_2$; $DT = 9.24 + 8.38X_1 + 4.59X_2 + 4.45X_1X_2$; $Fr = 1.9725 – 0.7775X_1 – 1.1225X_2 + 0.6275X_1X_2$ for paracetamol and, $H = 118.8 + 12.35X_1 + 48.05X_2 – 1.7X_1X_2$; $DT = 8.375 + 1.125X_1 + 3.875X_2 – 0.375X1X_2$; $Fr = 1.08 – 0.22X_1 – 0.42X_2 + 0.08X_1X_2$ for chloroquine phosphate). Surface response curves and contour plots were constructed and the

optimum regions determined by superimposing the contour plots. The optimum values were re-transformed using the equation: Trans = [2A – (Max + Min)]/ Max – Min, where Trans is the transformed value, A is the actual value of the factor being transformed, and Max and Min are the maximum and the minimum values in the range of the factor being transformed, respectively. Granules of the optimum formulations (6.21% w/w of binder for paracetamol, and 1.386% w/w of binder for chloroquine phosphate) prepared had mean bulk densities of 0.41 and 0.508 g/ml, tapped densities 0.474 and 0.584 g/ml, Carr's indexes of 13.58 and 13.01% and Hausner ratios of 1.16 and 1.15 for paracetamol and chloroquine phosphate, respectively. Tablets compressed at compression force of 14 KN (paracetamol) and 16 KN (chloroquine phosphate) were compared with predicted values (H: 122 and 119N, DT: 15 and 8.5 minutes and Fr: 0.6 and 0.9% for paracetamol and chloroquine phosphate, respectively). Tablets prepared with the gum showed H of 132 and 116N for paracetamol and chloroquine phosphate, respectively, and Fr of 0.9% for both substances. For comparison purposes, chloroquine phosphate tablets were prepared with 5% w/v PVP solution and H values of 122N and Fr of 0.9% were obtained. The DTs of the tablets made with the gum were 13 and 9.3 minutes for paracetamol and chloroquine phosphate, respectively. Dissolution profiles of the tablets were within the acceptable ranges (≥ 80 and ≥ 75% of drug release in 30 and 45 minutes for paracetamol and chloroquine phosphate, respectively). The respective T_{50}s were 5 and 8 minutes. From the foregoing, it can be concluded that gum of *A. polyacantha* can be used as an alternative binder in tablet formulations.

1. INTRODUCTION

1.1 Gums

Originally, the term "gum" was probably applied to natural plant exudates that had oozed from tree barks and hardened upon exposure to air. Gums can be grouped into three major groups, namely, natural gums, modified gums and synthetic gums. Natural gums are found in a natural state such as the tree exudates or seaweed hydrocolloids. Examples include gum arabic, guar gum and gum tragacanth. Natural gums are produced in response to wounding (exudate gums) and extracted from seeds of some legumes (extractive gums). Examples of exudate gums are gum arabic from *Acacia spp*., gum tragacanth from *Asiatic astraglus spp*., gum karaya from *Sterculia spp.* and gum ghatti from *Anogeissus latifolia*. Examples of extractive gums include locust gum from *Certonia siliqua* and guar gum from *Cyamopsis tetragonolobus* [1].

Modified gums, these are chemically modified natural gums or derivatives of naturally occurring materials such as cellulose or starch. Synthetic gums are completely synthesized chemical products such as polyvinylpyrolidone (PVP) and ethylene oxide polymers.

Gum arabic (acacia, Mwt. 240,000 – 580,000) is dried gummy exudate from the stems and branches of *Acacia senegal* (Linné) Willdenow or other African species of acacia (fam. Leguminosae) and it has been used since ancient Egyptian times by local people [2,3].

1.2 Botanical characteristics of some acacia species

A hundred or more species of acacia alone are known to yield gum, including those that are commercially important for gum arabic. *Acacia senegal* is the source of most gum arabic of

international trade. It is a shrub or tree up to 12m high, bark grey, scaly and rough. Prickles just below nodes in threes, up to 7mm long, the central one hooked downwards. The leaves are petiole grandular, leaflets 8-18 pairs, 1-7mm long, 0.5 – 1.75mm wide. The flowers are white or cream, in spikes 2-10cm long, normally produced with the leaves. Pods are straight dehiscent (open by splitting at maturity), yellowish brown to brown veined. Seeds are subcircular 8-12mm in diameter, areole 2.5-6X2.5-5mm.

A. seyal, Del, also a source of gum arabic, is a tree up to 9 m high with usually flattened crown; young branchlets almost glabrous. Leaves 3-7 pairs and leaflets 11-20 pairs. Flowers are bright yellow in heads. pods are constricted between the seeds, dehiscent 7.2x0.5-0.9 cm, finely longitudinally veined glabrous. Seeds are elliptic compressed 7-9x4.5-5, areole 5-6x 3.5mm. *A. seyal* has two varieties, var. seyal and var fistula.

A. polyacantha is a tree up to 21m high, trunk with fissured bark and knobby persistent prickles in pairs just below each node. Leaflets 0.4 – 0.75mm wide, not especially pale or glaucous beneath, normally midrib alone and sometimes some faint basal nerves visible beneath. The flowers are white or cream in spikes 3.5-12.5cm long produced with the new leaves. Pods are straight, dehicent brown veined. The seeds are subcircular 7-9x6-8mm in diameter, areole 3-4x2.5-3.5mm [4,5].

1.3 Botanical source and location of gums

About 500 species of acacia are distributed over tropical and subtropical areas of Africa, India, Australia, Central America and South west of Northern America, but only a comparatively few are commercially important. These include: *A.senegal, A. seyal, A. polyacantha, A. drepanolobium, A. karoo, A. paoli, A. late, A. dudgeoni, A. goourmaensis, A. macrostachya, A. macrothyrsa, A.nilotica, A. sieberana, A. raddiana, A. tortilis* and *A.*

ehrenbergiena. The important producing areas are the Republic of Sudan, Senegal and several smaller neighbouring African countries: BurkinaFaso, Mali, Mauritania, Kenya, Zimbabwe, Nigeria, Ghana, Chad and Niger. *A. senegal, A.seyal* and *A. polyacantha* have widespread distribution within the gum belt. Other species have limited regional distribution. For instance, *A. drepanolobium* and *A. paoli* is confined to Eastern Africa and the Horn of Africa while *A. late* and *A. dudgeoni* are confined to West Africa [6]. Grades of Kordofan gum (in Sudan) which are clear, white (sun bleached) and tasteless are preferred for food and pharmaceuticals [2,6].

1.4 Collection, production and quality of gums

Almost all of the world output of gum arabic is from the sub-Sahara or Sahel Zone of Africa. More than 90% of commercial gum arabic is collected from wild trees. The gum is collected by natives who scar (tap) the tree with a knife, then return days later to remove the tear of gum that has formed on the scar. There is a definite collection season, with variations in the physical properties of the exudate as each season progresses, and with a slight variation from year to year. The collection of gum commences in September and terminates at the end of June or before the onset of the rainy season [7,8].

Gums from different species exhibit characteristics that are intrinsically different. Even within the same species, different varieties produce gums with different characteristics. Besides botanical sources, season of collection, harvest and post-harvest treatment also affect quality. Included in this are the methods of harvesting, cleaning, sorting and grading practices. Tapping for example gives more consistent and better-formed gum than collection caused by insect borers. Better quality gum is obtained by picking it off the tree rather than letting it fall

on the ground. Above all, mixing the gum from different species at collection time or at post-harvest handling stage results in variability and is the prime reason for poor quality [9].

1.5 Physico-chemical properties of gums

1.5.1 Chemical properties

Chemically, the natural gums are acidic complex polysaccharides composed of salts of sugars other than glucose: L-arabinose, D-galactose, L-rhamnose and D-glucuronic acid combined with certain metallic cations such as sodium, potassium, calcium and magnesium [1]. For the most part, these gums have highly branched structures containing the different sugar units with many possible variations as regard to degree of branching, length of branches and type of linkages. Therefore, an almost infinite number of structures are possible. Forces act between molecules, between different parts of the same molecules and between polymer and solvent. These forces include hydrogen bonding, ionic charges, dipole and induced dipole interactions and van der Waals forces. All these forces affect properties as gel forming tendency, viscosity and adhesiveness.

Minimum standards for good quality gum arabic have been defined in the USP [3] as total ash, not over 4%; acid insoluble ash, not over 0.5%; water, not over 15%; heavy metals (as Pb) less than 4 ppm; insoluble residue, less than 1%.

1.5.2 Physical properties

The physical properties of gums are of first importance in determining their uses and their commercial value.

1.5.2.1 solubility

Gum arabic is unique among the natural hydrocolliods because of its high solubility in water. Gum arabic consists of three water-soluble fractions namely an arabinogalactan (±90%) and two arabinogalactan-protein complexes, which differ in their molecular size and in the proportion of the proteinaceous material associated with each [6]. Most common gums can not be dissolved in water at concentration higher than about 5% because of their high viscosities. Gum arabic however dissolves readily in cold water up to 50% concentration to give a tacky but not very viscous solution. Gum arabic is insoluble in alcohol and other organic solvents. It is slightly soluble in aqueous alcohol with the solubility decreasing as the proportion of alcohol to water increases to about 60% alcohol, at which level it is practically insoluble. Trivalent metallic salts will cause precipitation of gum arabic. Solution of gum arabic is incompatible with soap making emulsion [8].

1.5.2.2 Colour and form

Gums as seen or collected in the natural state are represented in a variety of shapes and forms. They are available in spheroidal tears up to 32mm in diameter, crystals, granules, powder (by mechanical process), spray and roller dried powder. The surface of most gums when fresh is perfectly smooth, but this may soon become rough or covered with minute cracks or striations due to weathering. The colour of gums (in the solid state) varies from almost white through various shades of yellow, amber and orange to dark brown. Colour is of great importance in the commercial valuation of gums. Some of the best grades of gum arabic are almost colourless, possessing faint traces of yellow. On the other hand, dark, brownish-black or even black gums sometimes occur [10].

1.5.2.3 Rheological behaviour

Although there is no report on the rheological behaviour of gum obtained from *A. polyacantha*, solutions containing up to 40% can be obtained from gum arabic due to its highly branched, compact structure, which still exhibit typical Newtonian flow behaviour. Viscous solutions are obtained only at concentrations greater than 40% where effective molecular overlap begins to occur and solutions gradually assume pseudoplastic behaviour denoted by a decrease in viscosity with increasing shearing stress [8,11].

Viscosity or thickness of a solution that a gum forms with water is of paramount importance in determining the quality of gum. The higher the viscosity the better the gum. Temperature and method of preparation affect the viscosity of acacia solution [12]. The viscosity is inversely proportional to temperature. Electrolytes tend to reduce the viscosity of gum arabic solution [8]. The tenacity (tensile strength) of gums is usually considered along with viscosity, the greater the tenacity the greater its value. The value of gums for adhesive purpose is dependent upon this character [7].

1.5.2.4 Specific gravity, moisture content and hardness

Specific gravity of gums range between 1.35-1.49 (sample dried at 100 ^{0}C are heavier). Gums vary in hardness. Hardness is obviously governed partly by the amount of moisture present, which ranges between 13-15%. USP limits 15%. Materials containing less than 12% chip easily and produce dust during transportation [2,7]. Most gums break with clear glassy fracture when properly dried and may be readily pulverized, a form in which they are frequently used [7].

1.4.2.5 Ageing

Age of the gum, i.e., the length of time it has remained attached to the tree after secretion may affect some of its physical properties. The colour of the gum may change from white to brown or dark-brown. The hardness may also change. Gums should be kept in dry places. Dilute gum arabic solutions of the same temperature and concentration have the same viscosity until the appearance of bacterial growth that usually appear in 36-48 hours after the solution is prepared [12,13].

1.6 Biological and toxicological properties

Gum arabic is widely used in the food and drug fields. It is non-toxic odourless, colourless, tasteless, and does not affect the colour, odour or flavour of the food or drug it is used in [8,14,15]. It is in the GRAS (Generally Recognised As Safe) list under the Federal Food, Drug and Cosmetic Act. It is generally agreed that gum arabic has a low level of digestibility and in a food it will not contribute to calorie intake [6,8,16].

Gum arabic contains both oxidases and peroxidases that may affect preparations containing easily oxidized substances. The enzymes can be inactivated by heating the gum solution to 80^0C or higher for 1 hour or autoclave the powder at 121^0C for a short time (about 15 minutes) [3,17].

1.7 Uses of gums

Natural polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. In pharmaceutics, gums are used as a stabilizer for emulsions,

binder and coating for tablets, and as an ingredient in cough drops and syrups. Ray et al. [18] prepared gum arabic pellets from which sustained release of ferrous sulphate was achieved. A soothing and softening agent, gum arabic is extensively employed in folk medicines. Among many other, it is used internally for coughs, diarrhoea, dysentery, haemorrhage and externally to cover inflamed areas. In food industries, it is used as a flavour fixative and emulsifier, to prevent crystallisation of sugar in confections. In cosmetics, as an adhesive for facial masks and powders and to give a smooth feel to lotions [7,19].

1.8 Tablet excipients

The characterisation of pharmaceutical excipients using a material science approach has helped in the design of drug formulations to obtain a desired set of performance properties [18]. The ingredients or excipients used to make compressed tablets are numerous and can be classified by their use or function as: fillers, binders, disintegrants, lubricants, glidants, wetting agents, antioxidants, preservatives, colouring agents and flavouring agents.

Fillers, binders, glidants and lubricants help to impart satisfactory processing and compression characteristics to the formulation. Disintegrants, wetting agents, antioxidants, preservatives, colouring and flavouring agents help give additional desirable physical characteristics to the finished tablets. It is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability and the process by which the dosage forms are prepared. This calls for the need for acquiring more information and use standards for excipients [20].

1.8.1 Pharmaceutical binders

Pharmaceutical binders are materials added dry or in liquid form to form granules or to promote cohesive compacts for directly compressed tablets. These include natural gums, alginic and alginates, starches, liquid glucose, cellulose derivatives and polyvinylpyrolidone.

Natural gums

Acacia and tragacanth are natural gums employed in solutions ranging from 10-25% concentration alone or in combination. These materials are more effective when they are added as solutions than when they are added dry to a direct compression formula. These natural gums have the disadvantage of being variable in their composition and performance based on their origin and they are heavily contaminated with bacteria. Therefore their wet granulation masses is quickly dried at a temperature above 37^0C to reduce bacteria proliferation [21]. Literature survey could not reveal the effect of gum of *A. polyacantha* as tablet binder but other gums have been evaluated. Guar gum, which is extracted from seeds of some legumes [22], is also used as binder at concentrations up to 10%. It possesses chemical properties typical of a polysaccharide [23]. The seed galatomannan of *Leucaena leucocephala* Lam. De Wit var. K-8 (Fam. Leguminosae), a natural polysaccharide, with properties comparable to guar gum, was also evaluated as a pharmaceutical binder. The seed gum compared well with standard pharmaceutical binders (starch, PVP K30) [24]. The effectiveness of a gum obtained from the cormels of *Colocassia esculenta* was evaluated comparatively with acacia and methylcellulose as binders in the formulation of poorly compressible drugs, paracetamol and metronidazole. The new polysaccharide gum showed better concentration-strength profile than acacia while methylcellulose yielded mechanically more stable tablets than the two binders did. The *in vitro* availability characteristics showed

that tablets produced with the new gum show acceptable disintegration and release profile within a certain range of its concentration in tablets [25].

Alginic acid and alginates

Alginic acid is a hydrophilic colloid extracted with dilute alkali from various species of brown seaweed (phaeophyceae). It is odourless and tasteless. It is best incorporated or blended into a tablet granulation by dry mixing processes up to a concentration of 1 – 5% [23]. Sodium alginate is the sodium salt of alginic acid which is easily gelled in the presence of a divalent cation as calcium ion [19].

Starches

Starch, in the form of paste or mucilage, has long been the most common granulating agent since the introduction of conventional tablet formulation [21]. Its use is based on its adhesive, thickening, gelling, swelling and film forming properties as well as its ready availability, low cost and controlled quality. Potato and maize starch are widely used in Europe and the USA. Despite its wide use, the effects of starch paste preparation add variables on granulation or tableting quality. Viscosity or thickness of the paste is one variable [26]. The pre-gelatinization degree of starch paste influences the properties of the resulting tablets [27,28]. A properly made paste is translucent rather than clear (which would indicate virtually complete conversion to glucose) and produces cohesive tablets that are readily disintegrated when properly formulated [26]. Concentration of starch paste varies from 10 – 20% [21].

Starches from different botanical sources may not have identical properties with respect to their intended use. Indeed the chemical composition and physical characteristics of a starch are typical of its biological origin. Hence the starch from each plant source will vary somewhat in appearance, composition and properties [29]. Some starches from local origin have been evaluated in this regard. Enset starch (composition on dry weight basis: 0.16% ash, 0.25% fat, 0.35% protein and 99.24% starch)[29], obtained from *Ensete ventricosum*, Musaceae, has been evaluated as tablet binder using chloroquine phosphate, dipyrone and paracetamol as model drugs. The results showed that enset starch had better binding ability and less disintegrating power than potato starch giving tablets of lower porosity [30, 31]. Dioscorea starch (composition on dry weight basis: 0.1% ash, 0.5% protein, 1% fat and 98.4% starch)[32], obtained from *Dioscorea abysinica*, Dioscoreaceae, was also evaluated as tablet binder. It showed better binding ability to that of maize starch and exhibiting somewhat lower crushing strength and higher porosity [33]. The binding performance of starches obtained from taro *Colocassia esculenta* Scholt and sweet potato tubers *Ipomoea batatas* Lamk was found to be similar to that of commercial cornstarch [34]. Starches obtained from the seeds of *Sorghum bicolor*, Moench, performed as well as maize starch and better than acacia in binding properties [35]. The uses of other alternative starches from rice [36], barley and wheat starches [31]; plantain starch from *Musa paradisiacia*, Musaceae [37]; and tapioca, dried fibrous remnant material obtained from cassava, *Manihot utilissima* [38-40] have also been extensively reported in various tablet formulations.

Liquid glucose

Liquid glucose is prepared by the incomplete acidic or enzymatic hydrolysis of starch [23]. It is a 50% solution in water, and is a fairly common wet granulating agent at concentrations of 5-10%.

Cellulose derivatives

Various cellulose derivatives have been used as binders in solution form. Carboxymethylcellulose (CMC), methylcellulose (MC), ethyl cellulose (EC), hydoxymethylcellulose (HMC), hydroxypropylcellulose (HPC), hydroxypropyl methylcellulose (HPMC)) are common binders and adhesives [26]. HPMC has been widely used in this regard. It is more soluble in cold water than hot. Other water-soluble cellulosics such as HPC have been used successfully in solution as binder at concentration 2 – 4%. HPC may also be used as an alcohol solution to provide an anhydrous adhesive [21]. Not all cellulosics are soluble in water. EC can be used effectively when dissolved in alcohol or as a dry binder, which then is wetted with alcohol. It is used as a binder for materials that are moisture sensitive. A fibrous cellulose obtained from sugar-cane bagasse has also been evaluated as tablet binder [41].

Polyvinylpyrolidone

Polyvinylpyrolidone (PVP) is a synthetic polymer that is used as an adhesive in either an aqueous solution or alcohol. This versatility has increased its popularity [21]. Its concentration ranges from 0.5 - 5% solution [23].

Many traditional materials compete successfully today after almost a century of effects to replace them. It is the usual balance of economics and performance that determines the

commercial reality. Natural polysaccharides do hold advantages over the synthetic polymers, generally because they are non-toxic, less expensive and freely available. Natural gums can also be modified to have tailor-made materials for drug delivery systems and thus can compete with the synthetic biodegradable excipients available in the market [18].

Methods of incorporation of binders

Tablet cohesion is best achieved when the binding component is used in solution as an adhesive [21,42]. In solution form, the binder is well distributed in the other materials of the tablet and results in better bonding with a lower concentration of binder [43,44]. Moreover, since powders differ with respect to the ease with which they can be wetted, and their rate of solubilization, it is preferable to incorporate the binding agent in solution [20]. Some poorly compressible drugs like paracetamol, metronidazole and acetazolamide can be successfully tableted only when a liquid adhesive and wet granulation procedure is employed [25,45]. 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 of time during granulation. Binder solutions are usually made up to weight rather than volume. This enables the formulator to determine the weight of the solids, which have been added to the tablet granulations in the binding solution.

1.8.2 Other excipients

Diluents are fillers designed to makeup the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. Disintegrants facilitate a breakup or disintegration of the tablet when it contacts water. Lubricants and glidants have overlapping functions.

Lubricants reduce the friction during tablet ejection between the walls of the tablet and the die cavity while glidants are intended to promote flow of the tablet granulation. Colouring and flavouring agents are used for disguising of off-colour drugs, product identification and production of a more elegant product [26].

1.9 Granulation

For the powder mixture to flow evenly and freely from the hopper into the dies, it is usually necessary to convert the powder mixture to free flowing granules. A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. The strength of a wet granule is due mainly to the surface tension of the granulation liquid and capillary forces. These forces are responsible for initial agglomeration of the wet powder. Granulation usually refers to processes whereby agglomerates with sizes ranging from 0.1 to 2mm are produced. The most important reasons for a granulation step prior to tableting are to improve the flow properties of the mix and hence the uniformity of the dose, to prevent segregation of the ingredients in the hopper of tablet machines, to improve the compression characteristics of the tablet mixture and to reduce dust during handling. There are various techniques of producing granules such as dry and wet granulation, extrusion [46,47] or spray drying.

1.9.1 Dry granulation

Dry granulation is a valuable technique in situations where the effective dose of a drug is too high for direct compaction and the drug is sensitive to heat, moisture or both, which precludes wet granulation [26]. The blend of powders is forced into dies of a large heavy-duty tableting press and compacted to slugs. The slugs or roller compacts are then milled and screened in

order to produce a granular form of tableting material which flows more uniformly than the original powder mix [48].

1.9.2 Wet granulation

Tableting by the wet granulation process is the most widely used method for pharmaceutical materials. This is accomplished by adding a liquid binder or an adhesive to the powder mixture, passing the wetted mass through a screen of the desired mesh size, drying the granulation and then passing through a second screen of smaller mesh to reduce further the size of the granules. Granulation was mainly performed in planetary mixers with low speed and low shear forces. Now there is a trend toward using machines that can carry out the entire granulation sequence in a single piece of equipment – the mixer- ganulator – dryer. Example is the fluidized bed granulation. Advantages of these machines include reduced handling of excipients, reduced exposure of excipients to heat, and a better opportunity to precisely control the moisture level in the granulation and reduced granulation time [49]. High shear mixers are also recently introduced with short process time and production of very dense granules with low porosity [46,50-52].

In wet granulation, liquid bridges are developed between particles, and the resulting tensile strength of these bonds increases as the amount of liquid increases. During drying, inter-particulate bonds result from fusion or recrystallisation and curing of the binding agent. The formation of crystal bridges has been shown to be a major influence on the physical characteristics of tablets especially if the solid is more soluble in the granulating fluid [30,36].

1.10 Direct compression

Although this is not a granulation method, some drugs like aspirin require the addition of direct compressible diluents such as microcrystalline cellulose, dibasic calcium phosphate. Dry methods and in particular direct compression are superior to those methods employing liquids, since dry processes do not require the equipment and handling expenses required in wetting and drying procedures and can avoid hydrolysis of water-sensitive drugs. Tablets are produced by mixing the drug with the compression vehicle in a blender. The powder mix is then compressed directly on a tableting machine. Direct compression vehicles should be free flowing, physiologically inert, tasteless, colourless, and have a good mouth feel [48].

1.11 Variables that affect granulation properties

The pharmaceutical elegance and ease of compression of tablets are related directly to the granulations from which the tablets are compressed. Granulation quality in turn, is dependent on the materials used (formulation), processing techniques and equipment employed [42,53,54]. Of these variables, the materials used especially the binding agent employed are fundamental to granulation particulate size uniformity, intergranular porosity, adequate hardness, compressibility and general quality. Binders are evaluated on different bases, such as mechanical properties of films, granules, tablets, and compressional properties of granules [20].

1.11.1 Effect of binders on granule properties

None of the pharmaceutical ingredients is more fundamental than the binding agents used in the formulation of granules. Most binding agents used for wet granulations, such as starch paste, acacia mucilage, gelatin solution, simple syrup, methylcellulose solution and corn

syrup are hydrophilic in nature. These binders increase the bulk density and reduce the porosity of the powder, thereby diminishing the effective surface area for evaporation. Hydrophilic binders also retard the rate of evaporation of moisture by lowering the vapour pressure of liquid moisture. In addition, the amount of moisture introduced into the granules and retained by them after drying varies greatly with different binding agents. 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 [55].

Many studies have been done on the effect of different binders: acacia, gelatin, PVP, HPC, methylcellulose solution, Eudragit at various concentration on the mechanical and physical properties of granules and correlating these with the characteristics of the corresponding tablets [20,25,56-58]. It was found that increasing the binder concentration was followed by an increase in the mean particle size, harder granules, decreased granule flowability and reduction in tapped density and hence reduction in granule porosity [59-63]. The reduced flow rate of granulations produced at higher binder concentrations is associated with the increase in their average size. Investigations on the effects of using different grades of PVP and gelatin binders in granules also showed that increasing the molecular mass of binder (or bloom number for gelatin) resulted in a decrease in granule friability but in an increase in granule size and porosity [64,65].

The most significant changes in the physical properties affected by binder dilution were found in granule friability and bulk density. Specifically, the more dilute binder solution resulted in less friable granules. Also considerable influence was observed on interparticulate porosity and thus on flow rate while insignificant effects was observed on average particle size and

granule density [66]. A change in the intraparticulate pore spaces of the granules is needed to effect change in granule density [67].

The mechanical properties of the granules and the corresponding compacts are basically determined by the physicochemical interactions of the substrate-binder interfacial layer [68,69]. The mechanical properties of granules and subsequent compacts were correlated with the physicochemical characteristics (contact angle, surface tension and binder concentration) of the granulating liquid made of PVP. Results indicated that the mechanical properties of the single particles as well as of the compressed compact increased when the binder concentration in the granulation liquid increased until a certain limit above which the increasing granulation contact angle hindered the binder spreading, creating weak regions in the compact and decreasing its mechanical strength [70-73].

1.11.2 Effect of processing variables on granule properties

Granule characteristics are reported to be influenced by equipment employed and processing variables such as method of granulation, volume of granulating fluid, massing time and method of compressing the granules to tablets [74,75].

Investigations on influence of various processing variables (impeller speed, granulating solution addition rate, total amount of solution added in the granulation step, 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 enhanced by the increase in the amount of added water, high impeller speeds and short wet massing time [76]. It was also found that moisture content had the

largest impact on granulation compressibility. Increasing wet massing time decreased granule porosity and fragmentation propensity hence increased granule strength, which led to granulation compressibility. It was reported granulation compressibility was extremely sensitive to processing conditions [50].

Process variables associated with the fluidized bed granulation technique include binder solution addition rate, air pressure to the binary nozzle, inlet air temperature and nozzle position with respect to the fluidized solids. When the rate at which the aqueous binder solution added to a fluidized bed of powders was increased, the ability of the solution to wet and penetrate the solids was enhanced, resulting in large average size, less friable granulation, a more fluid granulation and a decreased granulation bulkiness. Granule density was unaffected by varying the rate of binder addition [67,76].

Influence of drying temperature, drying process (tray- or freeze-drying), granulation liquid viscosity on the inter- and intra-granular drug migration were studied on both soluble and poorly soluble drugs. It was found that the drying temperature had no influence on the inter- and intra-granular drug distribution whereas a homogeneous distribution of drug in granules and in compacts was obtained by the use of freeze-drying. Intragranular migration was decreased as the granulation liquid viscosity increased [77-79]. It was also reported that fluidized-bed and infra-red dryers were found to have a 2- to 5-fold advantage in thermal efficiency and better physical properties over tray dryers in granule drying with the fluidized bed dryer being the most efficient [80].

The drying rate kinetics of pharmaceutical granulations depends on the physicochemical nature of the ingredients as well as the solutions of the binding agents used to form them [81]. Studies on granulations of lactose and sulfathiazole prepared using various commonly used binders: starch, gum acacia, corn syrup, CMC, povidone, gelatin and simple syrup showed that binders and diluents affected the drying rate curves of these granulations both qualitatively and quantitatively. Granules made with starch paste and gelatin solution required maximum time and energy for drying and those made with simple syrup USP required the least among the binders studied [55].

1.12 Granule flow

Studies indicate that the rheological behaviour of granules is closely related to tablet property [82]. Glidants and lubricants such as talc, magnesium stearate are added to promote flow of the tablet granulation. These glidants often possess a coefficient of friction less than that of the bulk solid and hence improve the flowability thereby decreasing interparticulate friction. Adequate mixing is needed for 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 had a measurable effect on granule flow. Granules with higher amount of fine (<100μ) and large particle size distribution will have poor flow from hoppers and will cause weight variation of the dosage form. This is mainly caused from the segregation of the fines. The smaller particles may fall through the voids between larger particles and thus make their way towards the bottom of the mass [48].

Many methods are available to measure the extent of interparticle forces as index of flow. Some of the more common are measurements of bulk density (poured density), angle of

repose, shear strength and hopper flow rate measurements. The former three are indirect measures while the latter is a direct measure of flow. Bulk density is the density calculated from the volume of a poured granule of known weight. Tapped density is calculated from the volume obtained by tapping the measuring cylinder mechanically at constant speed. A useful emperical guide is given by the Carr's compressibility index (1965), which is given by the equation:

$$\text{Carr's index (\%)} = [(\text{tapped density} - \text{bulk density})/\text{tapped density}] \times 100 \quad (1.1)$$

Carr's index of 5 – 15% indicate excellent flow, 12 – 16 good flow, and >23% indicate poor flow. A similar index has been defined by Hausner (1967) by the equation:

$$\text{Hausner ratio} = \text{Tapped density}/\text{bulk density} \quad (1.2)$$

Values less than 1.25 indicate good flow, while greater than 1.25 indicates poor flow [48].

Repose angle increases with increases in percentage of fines. Values for angles of repose < 30^0 usually indicate a free flowing material and angles ≥ 40^0 suggest a poorly flowing material. 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 binder was found to decrease hopper flow rates for three binders studied. The decreased hopper flow rates are a result of the increase in average particle size that occurs as formula weight of binder was increased [21]. However, at a constant formula weight of binder, increasing the granulating liquid used to granulate resulted in granules that gave a higher hopper flow rate [83].

1.13 Tablet compression

1.13.1 The process of compression

In pharmaceutical tableting, an appropriate volume of granules in a die cavity is compressed between an upper and lower punch to consolidate the material into a single solid matrix, which is subsequently ejected from the die cavity as an intact tablet. The subsequent events that occur in the process of compression are a) transitional repacking, b) deformation at points of contact, c) fragmentation and/or deformation, d) bonding, e) deformation of the solid body, f) decompression and finally ejection of the tablet. The process of compression is described in terms of the relative volume (ratio of volume of the compressed mass to the volume of the mass at zero voids) and applied pressure. This may be expressed by the Heckel equation in terms of relative density rather than volume:

$$\text{Ln } (1/(1-D)) = kP + A \qquad (1.3)$$

Where D is packing fraction of the tablet, P is applied pressure, constants k and A are determined from the slopes and intercepts respectively of the extrapolated linear portion of the plot of ln (1/(1-D)) vs P [83]. Materials have been characterised by comparing the behaviour of a material in the compression and decompression phase [84].

1.13.2 Compressional characteristics of granules

Information on the compression properties of drugs is extremely useful. Plastic materials deform by changing shape while there is very little permanent change in elastic materials during compression. While it is true that the tableted material should be plastic, i.e., capable of permanent deformation, it should also exhibit a degree of brittleness (fragmentation). Accordingly if the drug behaves plastically, the chosen excipients should fragment. If the

drug is brittle or elastic, the excipients should be plastic, or plastic binders could be used in wet massing [48].

Some materials like paracetamol are elastic. Paracetamol though fragmenting during compaction and consolidating by fragmentation to a large extent, its bonding capacity is very poor, paracetamol rebounds or elastically recovers when the compressive load is released. Paracetamol shows capping at higher compression forces and speeds [36]. If the dwell time under the compressive load is prolonged, then plastic deformation may continue leading to more consolidation. Information is obtained on elastic recovery during a compression cycle by measuring the expansion of the tablet after ejection. It was shown that the expansion of paracetamol tablets during compression was particularly sensitive to dwell time under a maximum load. Moreover, the extent and profiles of the elastic recovery curves were different for the tableting materials used [84].

Toughness is the ability to absorb energy without fracturing and is the resistance of materials to the propagation of cracks. Therefore, toughness of a material is defined as the energy needed to break a material; and materials with low toughness break very easily. Studies indicate HPC a non-ionic, water soluble cellulose ether with remarkable thermoplastic characteristics has a very high degree of plastic flow. Therefore, when HPC was used as a binder, it could provide strong toughness and absorb compression energy for preventing the capping of acetaminophen tablets. The same study showed capping and chipping occurred in tablets made with PVP, starch and MC [85].

There is also a report that starches deform mostly by plastic flow, which was dependent on particle size, size distribution and particle shape [85]. Potato starch showed plastic flow with ease, corn starch prone to plastic flow with little elastic recovery while barley and wheat were more elastically deformed than corn and potato starches [30]. PEG 3000 and PVP have low yield pressure value and relatively small elastic recovery value. Pregelatinized starch and microcrystalline cellulose (MCC) were found to have lower degree of deformity [86].

A granulating agent imparts a degree of plasticity to the particulate system, so that the formation of interparticulate bonds is favoured and tablet strength is enhanced [36,87]. The amount of bonding that takes place between the particles due to asperity melting and plastic and elastic deformation of the particles depends on the amount of binding agent present and the compression force applied [30]. It appears that the concentration of binder has a greater influence in more porous tablets than those approaching zero voids [88]. As the applied pressure is increased the porosity of the tablet is decreased, the interparticular distances through which bond forces operate are shorter and hence less amount of binder is used.

Studies on the role of the granulation moisture content on compression properties of granules made with selected binders (MC, povidone, pregelatinized starch, HPMC) showed that at lower pressures, higher-moisture containing granules were slightly more compressible than lower moisture containing granules. At lower pressures, the water lubrication effect did not occur but at higher pressures, the reverse was true because of the water lubrication effect [89]. It is also reported that at all compression speeds, an increase in moisture content reduced the percentage elastic recovery of HPMC compacts due to greater tablet consolidation [90].

1.13.3 Effect of compression force on tablet properties

Higuehi and Train [83] are probably the first pharmaceutical scientists to study the effect of compression on tablet properties and on distribution of pressure. The relationship between applied pressure and weight, thickness, density and the force of ejection are relatively independent of the material being compressed. Hardness, tensile strength, friability, disintegration and dissolution are properties that depend predominately on the formulation [83]. Tablets prepared at high forces are expected to exhibit smaller specific surface area, smaller porosity, higher tablet density and hardness and increased disintegration time than those prepared at low compression forces [91]. There is a linear relationship between tablet hardness and the logarithm of applied pressure except at high pressures. At higher compression pressures, the crushing strength reached a constant level [92]. Reports also indicate that a logarithmic connection exists between the pressing force and the porosity while the relation between the pressing force and the abrasion loss was a connection of power-function [93].

1.14 Tablet properties

Conventional tablets in general should have a certain amount of hardness, resistance to friability to withstand the rigors of mechanical shocks encountered during their production, packaging, transportation and handling prior to use. These tablet properties together with uniformity of weight, disintegration and dissolution depend on tabletting conditions employed, on size and distribution of the granules and predominantly on the formulation (granulation binding agent, moisture content)[83]. Generally, a correlation exists between the granules' properties and those of their compressed tablets [57,58]. Granules possessing best mechanical and physical characteristics will produce tablets with best pharmaceutical

property. It is apparent that the type and concentration of binder used in the granulation step would influence the corresponding tablet properties [38,62-64,94].

The effect of drying time, compression force, size of particles and moisture content of wet granules on tablet properties indicate that the formation and disintegration of tablets were related to the effect of the formation of solid bridges between particles. Several forces that can act between small neighbouring particles have been identified. Among these, van der Waals forces play the most important role in the formation of common compressed tablets. Hydrogen bonding and also moisture for tablets prepared by wet granulation method also play a key role in the tableting process [95].

1.14.1 Tablet hardness and friability

Hardness and friability are the most common measures used to evaluate tablet strength. Factors that may alter tablet hardness are alterations in machine speed, changes in particle size distribution of the granulation mix and lubricants. Dies having a light fill (large particles, low density) will produce a softer tablet than dies receiving a heavy fill (small particle, high density). Lubricants can have a significant effect on tablet hardness when used in too high a concentration or when mixed too long. The lubricants will coat the granulation particles and interfere with tablet bonding, reducing tablet strength [83,96]. It was also reported that the duration of lubricant mixing significantly changed the apparent bulk volume of the mix, ejection force during tableting, hardness and disintegration and dissolution properties of tablets [97]. The application method of lubricants also has influence on tablet hardness and ejectability after compression. It was found that mixing of lubricants with the granulation

gave better results for ejectability and hardness than the incorporation into the granulation [98].

1.14.2 Tablet tensile strength

The strength of a tablet may also be expressed as a tensile strength (breaking stress of a solid unit cross section in kg/cm^2). Tablet tensile strength, measured using the diametral compression test, allows the dimensions of the tablets to be taken into account while tablet hardness is only a measure of the force at which the tablet breaks. Since the radial tensile strength measurements considers the thickness of a tablet, and only tensile stress and axial tensile strength express the strength in the direction in which capping may occur, the tensile strength characterises the strength of a tablet more completely than hardness [99]. The radial tensile strength is expressed as:

$$\sigma_x = \frac{2F}{Dt\pi} \qquad (1.4)$$

in which F is crushing load, D is the diameter and t is the thickness of the tablet. The axial tensile strength is expressed as:

$$\sigma_z = \frac{4F}{D^2\pi} \qquad (1.5)$$

Reports indicate that flat-faced tablets have slightly higher tensile strength than deep biconcave tablets compressed to the same packing fraction [94]. Moreover, increasing the compression speed generally decreased the tensile strength of tablets [90].

In common compressed tablets, the number of contact points between particles plays important role in tablet tensile strength. With decreases in tablet porosity, the number of contact points increases, and tensile strength of the tablets shows a higher value. The tensile

strength was found to increase linearly with the log of porosity because more solid bridges are formed between particles [95].

Maximum tensile strength occurs when the tablet contained moisture between 2.5% and 4.5%, which is the optimum moisture range [100-104]. The increase in tablet hardness with increase in water content up to the optimum range could be attributed to the lubricating effect of water. Increasing the water content above the optimum range caused a reduction in tablet crushing strength due to the hydrodynamic resistance to consolidation [100,104].

1.14.3 Tablet disintegration and porosity

The importance of tablet disintegration was recognised as early as 1879 when a patent recommended that pills be perforated to admit gastric juice for better disintegration [105]. Complete tablet disintegration is defined as that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen of the test apparatus is a soft mass having no palpably firm core [3]. For tablets to be disintegrated, it is necessary to overcome the cohesive strength introduced into the mass by compression and by any binder present. It is therefore usual practice to incorporate a disintegrant, which will induce this process. Among the disintegrants, several types acting by different mechanism may be distinguished. Disintegrants that enhance the action of capillary forces in a rapid uptake of aqueous liquids and those that swell in contact with water are considered more important. Whatever could be the mechanism, to obtain rapid disintegration, a disintegrant force is generated by the replacement of solid/air with solid/liquid interfaces. The displacement of air by water or aqueous liquids is a wetting process that may lead to hydration of the involved particles [106]. Disintegrants can be incorporated extragranularly, intragranularly or distributed between the two phases.

Studies show that porosity, hydrophilicity, swelling ability of particles and interparticle forces are important factors for tablet disintegration. Tablet porosity is clearly related to water absorption, which is a very important step of the disintegration process. For conventional tablets, when tablet porosity is high, water can be absorbed easily and destruction of tablets is not very difficult. Disintegration is hardly affected by tablet formulation. However, when tablet porosity is not high, disintegration will be influenced by the properties of the excipients used [107]. The disintegration time of tablets were found to increase linearly with the log of porosity [95,108]. Generally, disintegration time increases with increasing compression force.

The wetability of the formulation plays a vital role in the process of disintegration and dissolution, which lead to release of the drug into the blood stream. Wetting is closely related to the inner structure of tablets and to the hydrophilicity of excipients [108]. The wetting and subsequent penetration of liquid into the capillary structure of the tablets are controlled, respectively, by the contact angle of the liquid on the solid surface θ, and by its surface tension γ and the pore radius. The adhesion tension ($\gamma\cos\theta$), which is a measure of tablet wetability, could be useful in providing information about the wetting and disintegration characteristics of tablet formulations [94,109,110]. Although disintegration is frequently considered a prerequisite for drug dissolution, it in no manner assures that a drug will dissolve and hence have the potential for satisfactory bioavailability [106].

1.14.4 Tablet Dissolution

A drug given in an orally administered tablet must undergo dissolution before it can be absorbed and transported into the systemic circulation. Although characteristics of granules by pore or void size analysis is useful in assessing the penetration of fluids into matrices, as well as compact strength, whenever a solid is in contact with a fluid particle, surface area is of paramount importance [59]. Disintegration of tablets plays a vital role in the dissolution process since it determines the area of contact between the solid and liquid [94,106]. On coming into contact with water, a tablet disintegrates into granules and then deaggregates into fine particles. Dissolution thus occurs from intact tablet, granules and fine particles. Assuming that the dissolution rate is proportional to the surface area available, the amount dissolved from the intact tablet will be negligible compared with that dissolved from the granules and fine particles. This has been described by Noyes and Whitney equation which is given by:

$$dc/dt = [AD/hv(Cs-C_t)] \quad (1.6)$$

where, dc/dt is the dissolution rate, A is surface area, D is diffusion coefficient, h is thickness of diffusion layer, v is volume of dissolution medium, Cs is the saturation concentration and C_t concentration at a given time t. It was also reported that T_{50} showed direct correlation with the disintegration time [59,94].

1.15 Effect of binders on tablet properties

Binders are added to a material to increase bonding. Granulations with a more homogenous distribution of binder in the granules generally produce tablets of a higher mechanical strength than granulations with a peripheral localisation of binder [96].

Studies on the effect of various formulations and processing factors on the properties of some tablets by various authors revealed that at a constant moisture level and packing fraction, an increase in binder concentration generally results in increased tensile strength, disintegration and dissolution times (decreased dissolution rates), reduced capping tendency, ER/PC (elastic recovery/plastic compression) ratio and the brittle fracture index value (BFI- a measure of the lamination tendency of tablets) of the tablets [86, 111-119]. Increasing molecular mass of binder (bloom number for gelatin for example) increases tablet tensile strength when compressed to fixed apparent density. The radial strength is little affected but the axial tensile strength is increased by increased concentration of binder to a strength greater than the radial strength. The results have been explained in terms of the effects of moist and binder bridges on bonding of particles in tablets [64,83]

The role of binders in the moisture-induced hardness increase in compressed tablets containing lactose as a major excipient was studied. Results showed that the increase in moisture-induced hardness in compressed tablets is related linearly to the amount of moisture loss from the tablets after compression [120,121]. It was also reported that the magnitude of the hardness increase is related to the type and concentration of the binder used in wet granulation [55]. This moisture-induced hardness increase in the tablets had no effect on the tablet disintegration time and *in vitro* drug dissolution [120,121].

1.16 The present study

Together with neighbouring countries, Ethiopia due to its diverse agro-climatic conditions has remained the natural home of various species of natural gums since time immemorial. Gum olibanum (from *Boswellia spp*.), gum myrrh (from *Commiphora spp*.), gum karaya (from

sterculia spp.) and gum acacia (from *A. senegal* and *A. seyal spp*.) are reported to yield gum and resin products of commercial value [10].

More than 40 species of the genus acacia are known to be indigenous to Ethiopia. But *A. senegl*, *A. seyal, A. polyacantha* (Gumero) and *A. drepanolobium* are the four species reported to yield economically important gums. Almost 100 percent of the existing gum and resin bearing trees under consideration are naturally and wildly grown under arid, warm or hot, very sloppy and rugged topographic conditions in almost all regions: Tigray, Amhara, Oromia, Gambella, Somalia, Benshangul, Southern Region and Afar in order of decreasing production area [10].

The binder properties of local gums of the *A. senegal* and *A. seyal* were evaluated and compared with acacia BP. It was reported that gum of *A. senegal* compared well with that of acacia BP as a binding agent (122,123). No work has been reported so far on gums of *A polyacantha*. The purpose of this study is to investigate the binding efficiency of a local gum obtained from *A polyacantha* species. This gum was used as a binder using two model drugs: Paracetamol, which is both sparingly soluble and poorly compressible drug, and chloroquine phosphate, which is a freely soluble drug.

1.13 Objectives of the study

General objective

The objective of the project is to evaluate the binding capacity of local gum of *A. polyacantha* in granules and tablet formulations.

Specific objectives

- To purify and determine the rheological behaviour of the gum;
- To prepare granules by wet granulation and determine their physical properties (size, size distribution, bulk density, tapped density, granule density, compressibility, intergranular porosity, granule friability and flowability);
- To determine properties of the compressed tablets namely, hardness (crushing strength), tensile strength, friability, porosity, disintegration time and dissolution rate;
- To optimise the binder concentration and compression force used to prepare the tablets using appropriate experimental designs;
- To prepare and compress tablets of the "optimum" formulation and compare with a standard binder, PVP.

2. EXPERIMENTAL

2.1 Materials

Gum of *A. polyacantha*, (two years old, from Gondar) was obtained from Natural Gum Processing and Marketing Enterprise. Paracetamol powder BP (batch no. P815, Srinivasa Agro Industries and Drug Ltd, India) and Chloroquine phosphate BP (batch no. 031111, Tianjain, China) were obtained from Addis Pharmaceuticals Factory, Adigrat. Croscarmellose sodium, NF (Ac-Di-Sol®) was obtained from FMC Corporation, PN, USA. Magnesium stearate was obtained from BDH Chemicals Ltd, Poole, England.

2.2 Reagents

Iodine TS was prepared according to USP [3], 14 g of iodine was added in 36 g KI in 100 ml of distilled water in which 3 drops of HCl was added and the resulting solution diluted to 1000 ml. Ferric chloride TS was prepared by dissolving 9 g of ferric chloride in water to make 100 ml.

2.3 Methods

2.3.1 Purification of the Gum

Gum of *A. polyacantha* was grinded into small pieces using mortar and pestle. The grinded gum was then dissolved in distilled water in 1:2 proportions. The dissolved gum solution was then strained and 60-70% v/v absolute ethanol was added to precipitate the gum from the aqueous solution. The gum was then washed and dried in an oven, Kottermann® 2711, Germany at 50 ^{0}C. The dried gum was grinded and powdered to fine particles and sieved through a 224 μm sieve.

2.3.2 Characterisation of the gum

The purified gum of *A. polyacantha* was characterised using methods described in the USP NF XXII [3]:

2.3.2.1 Determination of physico-chemical properties

Botanical Character: The odour, colour, surface texture of the gum was characterised.

Solubility: one gram of gum from *A. polyacantha* was dissolved in 2 ml of distilled water

pH: the pH of 50% of gum of *A. polyacantha* solution was checked with litmus.

Presence of starch or dextrin: 0.5% solution of gum of *A. polyacantha* was boiled and cooled and iodine TS was added to check for presence of starch or dextrin in the gum.

Test for tannin bearing gums: 0.1 ml of ferric chloride TS was added to 10 ml of 0.5% of gum of *A. polyacantha* solution to check for presence of tannins in the gum.

Water content: gravimetric method was used. Ten grams of the gum powder was accurately weighed and dried at 105 ^{0}C for 5 hours. The sample was weighed and weight loss calculated.

2.3.2.2 Rheological properties

Flow property of the gum powder

A standard glass funnel of 100 mm rim diameter; 60^{0} 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 from the bench surface. The outlet was covered and the funnel was filled with 50 g of the gum powder to the brim. The content was allowed to pour out and the time taken for the powder to flow through the orifice was recorded [22]. The flow rate and angle of repose were recorded and the values are averages of three determinations.

Flow property of the gum solution:

Gum solutions (25 ml) of various concentrations (5,10, 20, 30, 40%w/v) were prepared and their flow behaviour was compared with acacia using rotational viscometer, Searle type Cup and Bob viscometer (Rheotest 2.1/Rv 2.1 Device No. 6603, VEB MLW, Prufgerate-werk Medingen, Germany), measuring cylinder S/S_1 at room temperature. The sample was sheared at different shear rates in the space between the outer wall with a bob and the inner wall of a cup into which the bob fits. Their respective viscosities were determined from ratio of shear stress/shear rate, i.e.,

$$\eta = \tau / D \qquad (2.1)$$

where η is the viscosity in dynes.sec/cm^2 (=poise), τ is the shear stress in dynes/cm^2 and D is the shear rate in sec^{-1}.

The efflux time and the viscosities of the various concentrations were also determined using Redwood viscometer (Stanhope-SETA ltd. England) and Falling ball viscometer (Hoeppler viscometer B3, VEB MLW, Prufgerate-werk Medingen, Germany) respectively.

In Redwood viscometer, 25 ml of the gum solutions was put in the sample cylinder and the time needed for the gum solution to pass through the orifice was recorded and the values are average of three measurements).

In the Falling ball viscometer, two glass balls were used: ball one with density 2.227 g/cm^3 and ball constant 0.0107192 mPa cm^3/g and ball two with density 2.232 g/cm^3 and ball constant 0.077616 mPa cm^3/g. Enough amount of mucilage was put in the glass tube at room temperature and the time for the glass ball to pass between the marks (10 cm long) was recorded and the values are average of three measurements.

The viscosities of the respective concentrations were determined by the equation:

$$\eta = t\,(\delta_1 - \delta_2)K \qquad (2.2)$$

Where t is the time in second for the ball to pass between the two marks, δ_1 is density of the glass ball used, δ_2 is density of the gum mucilage under investigation and K is the ball constant.

2.3.3 Wet Granulations

2.3.3.1 Preparation of paracetamol and chloroquine phosphate granules

130 g of paracetamol powder or chloroquine phosphate powder was accurately weighed. Different concentrations (5, 10, 20, and 30% w/v) of mucilages of gum of *A. polyacantha* were freshly prepared and appropriate quantities of the mucilages (5-30% w/v for paracetamol and 5-20% w/v for chloroquine phosphate) were added to wet mass the powder using a mortar and pestle. Wet massing continued for 15 minutes. Amount of mucilage consumed was recorded for each batch. The wet mass was passed through a wet granulator (ERWEKA GmbH, type FGS, Germany) with 1.6 mm sieve and dried in an oven (Kottermann® 2711, Germany) at 50 ^{0}C for 20 hrs for paracetamol and an overnight (14 hrs) for chloroquine phosphate granules. The dried granules were screened by passing them through a 1mm sieve. The concentrations of binders added as granulating agents expressed in terms of the weight of dried binder for mucilages of 5, 10, 20 and 30% w/v were calculated to be 1.35, 2.7, 5.4 and 8.1% w/w for paracetamol and 0.77, 1.54 and 3.08% w/w for chloroquine phosphate granules. The screened granules were put in plastic bags at room temperature (20 ^{0}C) to prevent loss of moisture. Each batch of granules was done in triplicates.

2.3.3.2 Moisture content

Moisture content of the granules was determined gravimetrically by taking 5 g from each batch of the granules and heating the samples in an oven at 120 ^{0}C for 1 hour. The granules were weighed immediately and the loss in weight was considered as moisture content of the granules.

2.3.4 Characterisation of granules

2.3.4.1 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. The sieves were shaken at the same intensity for 2 minutes using the universal Drive unit (ERWEKA, Type AR 401, Germany). The granules remaining on each sieve were weighed and percent granules retained on each sieve recorded and mean granule size was calculated for each batch. The granule size distributions recorded are averages of three determinations.

The average granule size on any sieve was determined in microns by averaging the size of the openings of the sieve through which the granules passed and the size of the openings of the sieve upon which the granules were retained. The weight retained on each sieve was converted to percentage retention and multiplied by the average of two successive sieves. The sum of these products divided by 100 yielded an average granule size.

2.3.4.2 Determination of bulk, tapped and true density

Thirty grams of each batch of granules, ranging from 1 mm – 224 μm in size, were put in 250 ml measuring cylinder, the volume occupied by the granules was read to the nearest 0.5 ml and the bulk density calculated as g/ml.

The bulk in the cylinder was tapped using tapped densitometer (ERWEKA, type SVM, Germany), which provided a fixed drop of one-half inch at a rate of 250 taps/min. The volume occupied by the granules was recorded and tapped density was calculated.

The true density of the granules were determined by air compression pycnometer (Beckman GmbH, 8000 Munich, Germany) at room temperature using atmospheric air as compression gas. The instrument was calibrated using a small stainless steel ball weighting 65.9126 g and the correction factor determined by dividing the true volume with the measured volume (average of three measurements). Sample size of 2/3 of the volume of the pycnometer (approximately 13 g) was measured on analytical balance. After 10 minutes of equilibration time in the pycnometer the volume was measured. Measurements were made three times on the same sample. The samples were left in the pycnometer vessel for one hour before the next measurements were effected to allow the equilibration of the adsorbed gas. Averages of the measurements were recorded and the volume was corrected by the correction factor determined above. The true density of the granules was determined by dividing weight of sample by the corrected volume. Densities recorded are averages of five determinations.

2.3.4.3 Density related properties

The Carr's index (Percent compressibility) of the granules was calculated from the difference between the tapped and bulk densities divided by the tapped density and the ratio expressed as a percentage.

$$\% \text{ compressibility} = [(D_t - D_b)/ D_t]x\ 100 \quad (2.3)$$

where D_t is the tapped density, D_b is the bulk density.

The Hausner ratio was calculated by dividing the tapped density by the bulk density of the granule [120].

$$\text{Hausner ratio} = D_t / D_b \quad (2.4)$$

2.3.4.4 Determination of granule flow rate and angle of repose

Fifty grams of each batch of granules were poured in a standard glass funnel of 100 mm diameter; 60^0 bowl angle with a 91mm stem length and a 7mm internal stem diameter by the method described above (see 2.3.2.2). The time taken for the granules to pour out was measured. The flow rate and angle of repose were then calculated [22]. Granule flow rates and angle of repose recorded are averages of five determinations.

$$\text{Angle of repose} = \theta = \tan^{-1}(h / r) \quad (2.5)$$

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

2.3.4.5 Determination of granule friability

Ten grams of each batch of the granules larger than 315 μm was put in a friability tester (ERWEKA type TAR-20, Germany) and allowed to revolve for 5 minutes at 20 rpm dropping the granules a distance of 6 inches. The granules were then sieved using the 315 μm sieve and

percent loss was calculated as friability. Percent friability recorded is averages of four determinations.

2.3.5 Preparation of tablet formulations

Two hundred and fifty grams of paracetamol or chloroquine phosphate granules, ranging from 1 mm – 224 μm in size, were mixed with 4% Ac-Di-Sol® in a cube mixer (ERWEKA GmbH, type UG, Germany) for 10 minutes at 25 rpm. 0.5% magnesium stearate was then added and the mixture was mixed for further 5 minutes. The mixed granules were then compressed into tablets. Target tablet weights were 500 mg for both paracetamol and chloroquine phosphate. The tablet formulations for both substances are shown in the table below.

Table 2.1 Paracetamol and chloroquine phosphate formulations containing gum of *A. polyacantha* as a binder.

	Paracetamol	Chloroquine phosphate
Paracetamol (g)	130	-
Chloroquine phosphate (g)	-	130
Gum of *A. polyacantha*		
• % in mucilage	5 – 20	5 – 20
• amount of mucilage used (ml)	35	20
• % dry weight basis	1.35 – 5.4	0.77 – 1.54
Ac-Di-Sol® (%)	4	4
Magnesium stearate (%)	0.5	0.5

2.3.6 UV calibration curves of paraetamol and chloroquine phosphate

Stock solution containing 0.2 mg/ml of paracetamol in phosphate buffer pH 5.8 were prepared and diluted to six different concentrations (0.002, 0.004, 0.006, 0.008, 0.01, 0.012 mg/ml). The UV absorbance readings were taken at 243 nm using UV/visible spectrophotometer (Spectronic® Genesys 5, Milton Roy Company, USA). Phosphate buffer was used as a blank. The Beer-Lambert curve was drawn and correlation coefficients calculated. The same procedure and instrument was used for chloroquine phosphate except that stock solution of 0.5mg/ml in distilled water was prepared and diluted to concentrations of 0.005, 0.0075, 0.01, 0.0125, 0.015, and 0.0175 mg/ml. UV absorbance readings were taken at 343 nm and distilled water was used as a blank.

2.3.7 Experimental Design

The study of the binding property of the gum is based on an experimental design.

Target: to produce a tablet with reasonable hardness (80 – 140 N), minimum friability (<1%), Disintegration time less than 15 minutes and dissolution rate within the USP specification (80% dissolution within 30 min for paracetamol and 75% within 45 min for chloroquine phosphate).

Strategy: employment of design of experiments. A two-factor two-level experimental design was used. This has the advantage of increased information, performing fewer experiments and simplicity [124]. Binder concentration (X_1) and compression force (X_2) were taken as independent variables. To point out binder influence and compression forces on the properties of tablets, response variables such as tablet hardness (H), friability (Fr), and Disintegration time (DT) were selected.

A polynomial regression algorithm was used to relate the controlling factors to the response variables. The general first order model equation that could be constructed from the 2^n experimental design was [124]:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_1\beta_2 X_1 X_2 \quad (2.6)$$

Where Y is the measured response, β_0, β_1, β_2, and $\beta_1\beta_2$ are coefficients, and X_1, X_2 and X_1X_2 are the binder concentration, compression force and interaction term respectively.

The levels of the controlling factors were transformed to facilitate the calculation of the coefficients. Using the following equation [107]:

$$Trans = [2A - (Max + Min)]/ Max - Min \quad (2.7)$$

Where Trans is the transformed value, A is the actual value of the factor being transformed, and Max and Min are the maximum and the minimum values in the range of the factor being transformed, respectively.

Therefore, the operational definition is,

-1 = low 1 = high

Table 2.2 Transformed design matrix for analysis of responses of paracetamol and chloroquine phosphate tablets

Trials	Variables			Responses		
	X_1	X_2	X_1X_2	H	Fr	DT
1	-1	-1	1			
2	1	-1	-1			
3	-1	1	-1			
4	1	1	1			

The coefficients were calculated by the general formula [124]: $\beta = \Sigma XY/2^n$

Where β is the coefficient, X is the corresponding variable and Y is the response value (value of H, f or DT) and n is the level. For example, for Paracetamol, $\beta_0 = \Sigma H/4$ for calculation of β_0 in the response Hardness; $\beta_1 = \Sigma X_1 H/4$ for calculation of the coefficient of binder concentration in the response, Hardness; $\beta_2 = \Sigma X_2 H/4$ for calculation of the coefficient of compression force in the response, Hardness; $\beta_1\beta_2 = \Sigma X_1 X_2 H/4$ for calculation of the coefficient of the interaction term in the response, Hardness. The same method was used for the calculations of the coefficients in the responses f and DT, i.e., $\beta_0 = \Sigma f/4$ for calculation of β_0 in the response friability; $\beta_1 = \Sigma X_1 f/4$ for calculation of the coefficient of binder concentration in the response, friability; $\beta_2 = \Sigma X_2 f/4$ for calculation of the coefficient of compression force in the response, friability; $\beta_1\beta_2 = \Sigma X_1 X_2 f/4$ for calculation of the coefficient of the interaction term in the response, friability, and $\beta_0 = \Sigma DT/4$ for calculation of β_0 in the response Disintegration; $\beta_1 = \Sigma X_1 DT/4$ for calculation of the coefficient of binder concentration in the response, Disintegration; $\beta_2 = \Sigma X_2 DT/4$ for calculation of the coefficient of compression force in the response, Disintegration; $\beta_1\beta_2 = \Sigma X_1 X_2 DT/4$ for calculation of the coefficient of the interaction term in the response, Disintegration.

Similarly, for chloroquine phosphate, $\beta_0 = \Sigma H/4$ for calculation of β_0 in the response Hardness; $\beta_1 = \Sigma X_1 H/4$ for calculation of the coefficient of binder concentration in the response, Hardness; $\beta_2 = \Sigma X_2 H/4$ for calculation of the coefficient of compression force in the response, Hardness; $\beta_1\beta_2 = \Sigma X_1 X_2 H/4$ for calculation of the coefficient of the interaction term in the response, Hardness. The same method was used for the calculations of the

coefficients in the responses f and DT, i.e., $\beta_0 = \Sigma f/4$ for calculation of β_0 in the response friability; $\beta_1 = \Sigma X_1 f/4$ for calculation of the coefficient of binder concentration in the response, friability; $\beta_2 = \Sigma X_2 f/4$ for calculation of the coefficient of compression force in the response, friability; $\beta_1\beta_2 = \Sigma X_1X_2 f/4$ for calculation of the coefficient of the interaction term in the response, friability, and $\beta_0 = \Sigma DT/4$ for calculation of β_0 in the response Disintegration; $\beta_1 = \Sigma X_1 DT/4$ for calculation of the coefficient of binder concentration in the response, Disintegration; $\beta_2 = \Sigma X_2 DT/4$ for calculation of the coefficient of compression force in the response, Disintegration; $\beta_1\beta_2 = \Sigma X_1X_2 DT/4$ for calculation of the coefficient of the interaction term in the response, Disintegration.

2.3.8 Compression of tablets

The paracetamol granules were compressed approximately at 5, 10, 15 and 20 KN and chloroquine phosphate granules were compressed approximately at 10, 15, 20 and 25 KN on an instrumented eccentric tablet machine (EKO Korsch, 8410-68, Berlin, Germany) which was fitted with either 10 mm flat-faced or 11 mm diameter bevelled punches for paracetamol and 10 mm diameter flat-faced punches for chloroquine phosphate granules. The upper punch holder was instrumented with strain gauges. Signal transfer was achieved by a carrier frequency bridge. Compression data were collected and analysed using a program called *Messfix* [36]. The compression forces and the relative standard error were recorded. Compression forces recorded are averages of three recordings.

After ejection, tablet weight variation was determined for each batch and left for 24hrs at room temperature in glass containers before evaluation of their properties.

2.3.9 Evaluation of tablets

2.3.9.1 Crushing strength (H)

Ten tablets were taken and the crushing strength of the tablets was determined using hardness tester (Schleuniger,2E/205, Switzerland). Each tablet was placed between two anvils and force was applied to the anvils, and the crushing strength that just causes the tablet to break was recorded. Crushing strengths recorded are averages of ten tablets.

2.3.9.2 Tablet thickness & porosity

Tablet thickness was measured using a sliding calliper scale (Nippon Sokutei, Japan) which provides rapid and accurate measurements. Tablet porosity, $\in$, was calculated according to the method of Martin [68], using the equation

$$\in = (1-m/P_tV)x100 \qquad (2.8)$$

Where P_t is the true density in g/ml, m is the weight and V is the volume of tablet.

2.3.9.3 Tablet tensile strength

The radial tensile strength was calculated using the data obtained from crushing strength determination, diameter, and thickness of the tablets using equation (1.4) for radial tensile strength.

2.3.9.4 Friability determination (f)

Ten tablets of known weight from each batch were placed in the friability tester (ERWEKA, TAR 20, Germany) and were subjected to combined effects of abrasion and shock by placing

them in a plastic chamber that revolves at 20 rpm for 5 minutes. The tablets were then sieved and weighed. The percent loss in weight was calculated as friability.

2.3.9.5 Disintegration time (DT)

DT test was carried out according to USP specification. 6 tablets were placed in a disintegration tester (Pharmatest, PTZ-E, Germany) filled with distilled water at 37±0.2^{0}C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh. Disintegration times recorded are mean of two determinations.

2.3.9.6 Dissolution test

The dissolution test of paracetamol tablets was done according to the USP specification using dissolution apparatus Type II (Pharmatest, PTW II, Germany), with 900 ml phosphate buffer (pH 5.8) as the dissolution medium at 37± 0.5 ^{0}C which was stirred at a rate of 50 rpm. Distilled water (900 ml) was used as dissolution medium at 37^{0}C± 0.5 for chloroquine phosphate tablets.

Five millilitres of aliquots of the dissolution medium were removed at 5, 10, 15, 20, 30, 45 and 60 minutes and filtered using Whatman No.1 filter paper. Equal amount of fresh medium kept at the same temperature was transferred into the dissolution vessel. The filtered samples were appropriately diluted and absorbance readings were taken with UV/ Visible spectrophotometer (Spectronic® Genesys 5, Milton Roy Company, USA) at 243 nm (for paracetamol) and 343 nm (for chloroquine phosphate). Phosphate buffer was used as a blank for paracetamol and distilled water for chloroquine phosphate tablets. Cuvette (QS-100) used

was 1 cm for both paracetamol and chloroquine phosphate. All the necessary corrections for dilution were made when calculating the drug content.

2.3.10 Statistical analysis

The values of the coefficients obtained were subjected to equation (2.6), and surface response and contour plots of the corresponding responses were constructed using a programme called *Mathematica* [125]. The plots were analysed, and the "optimum" binder concentration and compression force values were then determined from the region obtained by superimposing the contour plots of the responses. The expected tablet properties of the optimum formulation were determined by substituting the values in equation (2.6). The optimum formulation was compressed to tablets and its properties determined. The actual results of the tablet properties were compared with the predicted ones.

2.3.11 Granulation and compression of the optimum formulation

2.3.11.1 Granulation of optimum formulation

Four-hundred grams of paracetamol powder or chloroquine phosphate powder was accurately weighed. 12% w/w (for paracetamol) and 4.26% w/w (for chloroquine phosphate) of mucilages of gum of *A. polyacantha* were freshly prepared and appropriate quantities of the mucilages were added to wet mass the powder using the Laboratory Kneader (Erweka GmbH, type LK5, Germany). Wet massing continued for 15 minutes. The wet mass was passed through a wet granulator (ERWEKA GmbH, type FGS, Germany) with 1.6 mm sieve and dried in oven (Kottermann® 2711, Germany) at 50^0C for 20hrs for paracetamol and an overnight (14hrs) for chloroquine phosphate granules. The dried granules were screened by passing them through a 1mm sieve. The screened granules were put in plastic bags at room

temperature (20 ^{0}C) to prevent loss of moisture. Granules of chloroquine phosphate were also done using 5% w/v PVP solutions for comparison. Each batch of granules was done in triplicates. Moisture content of each batch of the granules was maintained at 3.5 % for paracetamol and 4% for chloroquine phosphate.

2.3.11.2 Characterisation of granules

The granules were characterised using the same methods outlined on section 2.3.4. Data recorded are averages of three measurements.

2.3.11.3 Tablet compression and evaluation

Granules of paracetamol or chloroquine phosphate were mixed with 4% Ac-di-sol® for 10 minutes, and with 0.5% magnesium stearate for further 5 minutes using the cube mixer (ERWEKA, GmbH, type UG, Germany). The prepared granules were compressed using the afore-mentioned eccentric tablet machine. The tablets were then evaluated for tablet properties using the above methods (section 2.3.9). The results of the evaluation were compared with the predicted values obtained from the experimental design.

3. RESULTS AND DISCUSSION

3.1 Characterisation of gum of *A. polyacantha*

Physico-chemical properties

Gum of *A. polyacantha* was odourless, its colour ranging from white to yellowish brown and its surface texture glassy and sometimes opaque from the presence of numerous fissures.

50% of solution of gum of *A. polyacantha* was prepared and it was acid to litmus. 0.5% solution of gum of *A. polyacantha* did not show bluish or reddish colour upon addition of iodine TS, which implied that there was no starch or dextrin in the purified gum. Moreover no blackish colour or precipitate was formed when ferric chloride TS was added which also implied the gum does not have tannins.

The purified gum powder was found to have moisture content of 11.6% of its weight, which is within the pharmacopoeial specification (11-15%). It can be seen that gum of *A. polyacantha* met USP NF specifications set for acacia.

Rheological properties

Determination of powder flow rate is the direct measure of powder flowability. The gum powder was found to have an average flow rate of 485.7 g/min and repose angle of 30.1^0, which indicated good flow property.

The results of the rotational viscometer of the gum mucilages at different concentrations are shown in the Table 3.1. The rheograms or graphical representation of the data (Figures 3.1 and 3.2) show that the shear rates of all the mucilages are directly proportional to the shear stress. This means that gum of *A. polyacantha* exhibits Newtonian flow similar to Acacia BP for all the concentrations studied. For Newtonian systems, the higher the viscosity of a liquid, the greater the force per unit area (shear stress) required to produce a certain rate of shear. The

viscosities of the mucilages also shown in Table 3.1were obtained from the slope of the flow curves. The viscosity of gum of *A. polyacantha* was found to be lower than that of the Acacia BP for all the concentrations studied.

Since the gum showed Newtonian flow, investigation of the gum mucilages (5, 10, 20, 30 and 40% w/v) by falling ball viscometer and Redwood viscometer was necessary. Results in Tables 3.2 and 3.3 showed that the efflux time of mucilages of gum of *A. polyacantha* was lower than that of Acacia BP when compared for the same concentration. Consequently, the viscosity of the gum calculated in poise, using equation (2.2) was lower than that of Acacia BP. These results are in good agreement with the results obtained from the rotational viscometer.

Table 3.1 Rheological data of gum of *A. polyacantha* and Acacia BP measured with Searle type Cup and Bob viscometer at room temperature (20 ^{0}C)

Shear rate (sec^{-1})	Shear Stress (dynes/cm^2)									
	Mucilage concentration (w/v)									
	Gum of *A. polyacantha*					Acacia BP				
	5%	10%	20%	30%	40%	5%	10%	20%	30%	40%
48.6	1.8	3.4	8.26	34.47	83	2.2	4.3	9.7	30	88.93
72.9	2.6	5.1	12.4	48.2	124.0	3.3	6.4	14.8	45.4	133.4
81	3.0	5.6	13.77	53.8	137.7	3.7	7.0	16.2	45.4	148.23
121.5	4.3	8.5	20.66	73.8	206.5	5.5	10.7	24.3	50.4	222.35
145.8	5.2	10.0	24.79	82.5	247.9	6.6	12.8	29.0	75.7	266.8
218.7	7.8	15.2	37.2	117.3	372.0	10.0	19.2	43.7	136.3	400.22
243	9.0	17.0	41.3	126.0	413.0	11.0	21.0	48.5	151.4	444.69
364.5	13.0	25.0	61.97	183.5	619.5	16.6	32.0	73.0	227.0	667.04
437.4	16.0	30.0	74.36	216.8	743.6	20.0	38.4	87.8	272.5	800.44
656	23.5	46.0	111.52	311.9	1115.0	30.0	57.6	131.0	408.9	1200.48
Viscosity (dynes.sec/cm^2 =poise)	0.0360	0.0694	0.1700	0.5509	1.7001	0.0455	0.1027	0.2002	0.5856	1.8300

Table 3.2 Viscosity measurements of gum of *A. polyacantha* and Acacia BP mucilages using Falling ball viscometer at room temperature (20^0C).

	Mucilage Concentration (% w/v)										
	Distilled water	gum of *A. polyacantha*					Acacia BP				
		5	10	20	30	40	5	10	20	30	40
Average time (Sec)	101	276	550	174	599	2050	354	702	258	749	2298
Density of ball (g/cm^3)	2.227	2.227	2.227	2.232	2.232	2.232	2.227	2.227	2.232	2.232	2.232
Viscosity (poise)	0.013	0.036	0.070	0.156	0.517	1.70	0.046	0.088	0.219	0.623	1.88

Table 3.3 Efflux time of gum of *A. polyacantha* and Acacia BP mucilages using Redwood viscometer at room temperature (20^0C).

	Mucilage Concentration (% w/v)										
	Distilled water	gum of *A. polyacantha*					Acacia BP				
		5	10	20	30	40	5	10	20	30	40
Average time (Sec)	30.5	34	43	107	333	1015	41	60	163	455	1829

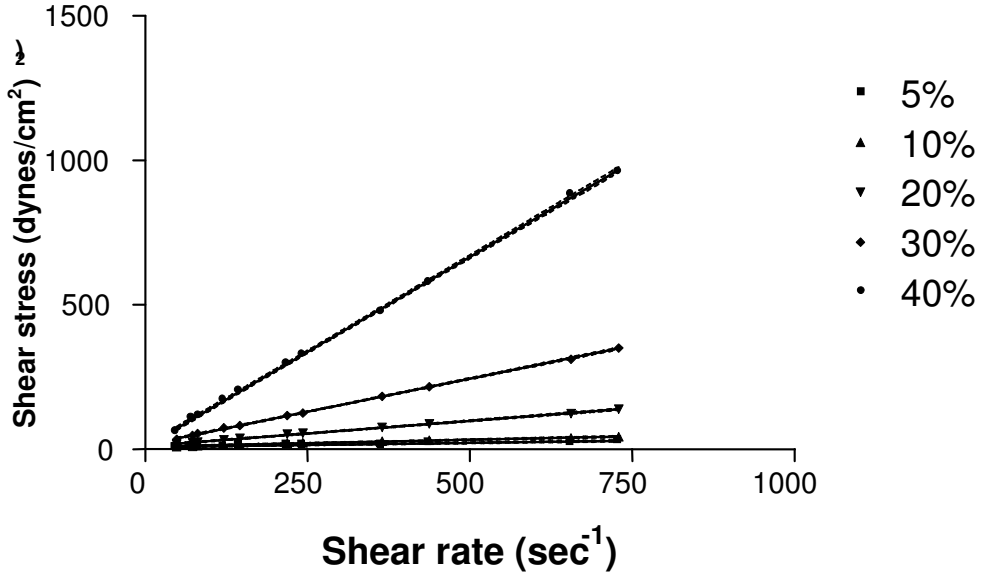


Figure 3.1 Rheogram of gum of *A. polyacantha* mucilages at different concentrations (w/v) at 95% confidence interval as measured by Searle type Cup and Bob rotational viscometer at room temperature (20 ^{0}C).

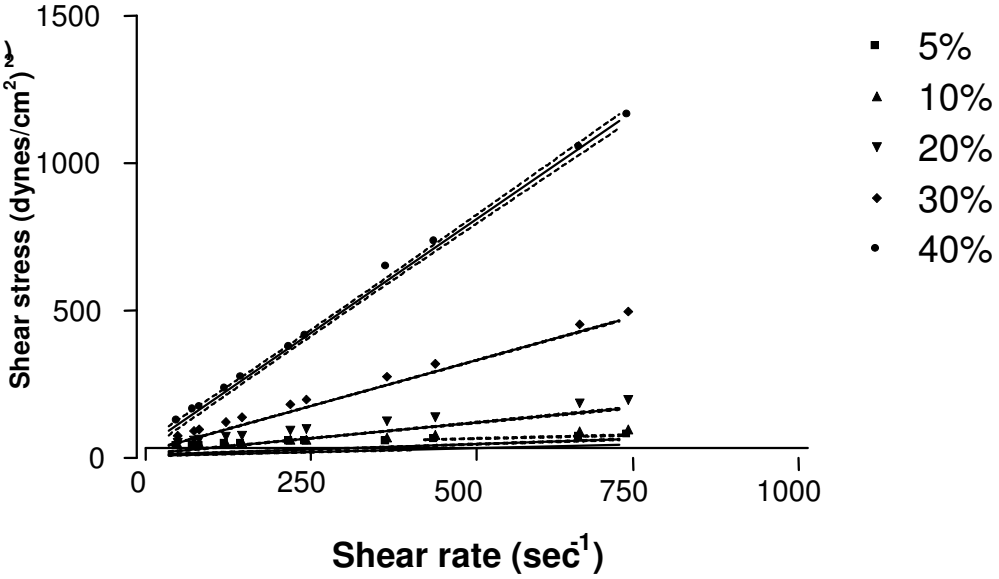


Figure 3.2 Rheogram of Acacia BP mucilages at different concentrations (w/v) at 95% confidence interval as measured by Searle type Cup and Bob rotational viscometer at room temperature (20 ^{0}C).

3.2Characterization of granules

The moisture content of paracetamol granules produced was maintained at 3% while moisture content of chloroquine phosphate granules was maintained at 4%.

3.2.1 Granule size distribution

Granule size distributions of the different binder concentrations are shown in Tables 3.4 and 3.5. Generally, good particle distributions were obtained for all the binders used. However, an increased in proportion of larger granules was observed with increased binder concentration. This is clearly seen in Figure 3.3. An increase in mean granule size was also noted with increase in binder concentration (Table 3.6). This growth in granule size may be attributed to an increase in penetration and wetting capabilities of the aqueous binder solution.

Particle size influences the production 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 [48]. Therefore a normal particle size distribution is necessary to reduce weight variation and maintain content uniformity.

Lower mean granule size was observed for chloroquine phosphate with binder concentration of 1.54% w/w. This weak correlation of mean granule size with increasing binder concentration could be due to processing variables such as changes in the rate of addition of binder concentration. It has been shown that a decrease in rate of addition of binder solution results in lower mean granule size [22].

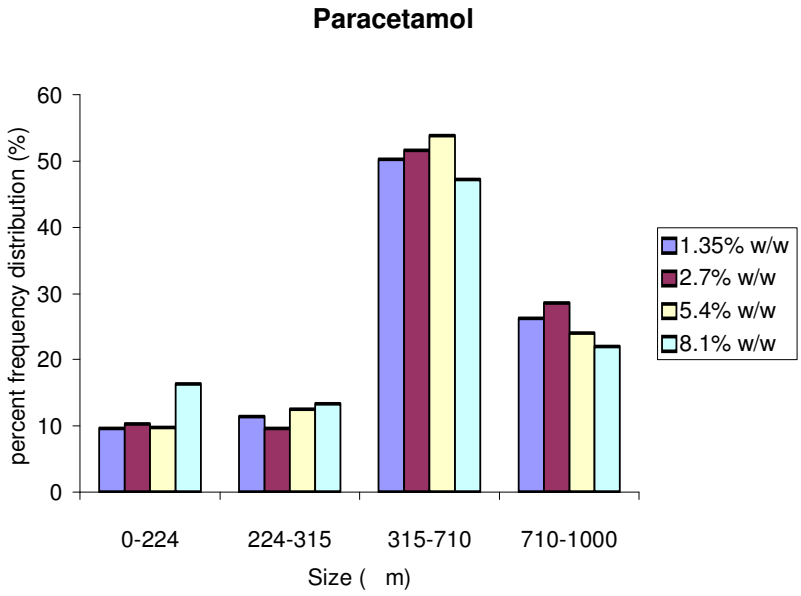
Table 3.4 Granule size distribution of Paracetamol granules prepared at different binder concentrations.

Sieve range (μm) Passed/retained	Mean size of opening (μm)	Weight of granules retained (g)				% Granules retained (g)			
		1.35% w/w	2.7 % w/w	5.4 % w/w	8.1% w/w	1.35% w/w	2.7 % w/w	5.4 % w/w	8.1% w/w
1000/710	855	7.88	8.55	7.2	6.84	26.27	28.50	24	22.8
710/315	512.5	15.06	15.47	16.13	14.16	50.20	51.56	53.77	47.2
315/224	269.5	3.4	2.9	3.75	3.98	11.33	9.67	12.50	13.3
224/pan	112	2.87	3.08	2.92	4.92	9.57	10.27	9.73	16.4

Table 3.5 Granule size distribution of Chloroquine phosphate granules prepared at different binder concentrations.

Sieve range (μm) Passed/retained	Mean size of opening (μm)	Weight of granules retained (g)			% Granules retained (g)		
		0.77 % w/w	1.54 % w/w	3.08 %w/w	0.77 % w/w	1.54 % w/w	3.08 % w/w
1000/710	855	9.32	6.59	9.79	31.07	21.97	32.63
710/315	512.5	14.92	15.73	15.31	49.73	52.63	51.03
315/224	269.5	2.55	3.67	2.39	8.50	12.23	7.97
224/pan	112	3.21	3.95	2.51	10.70	13.17	8.37

(a)



(b)

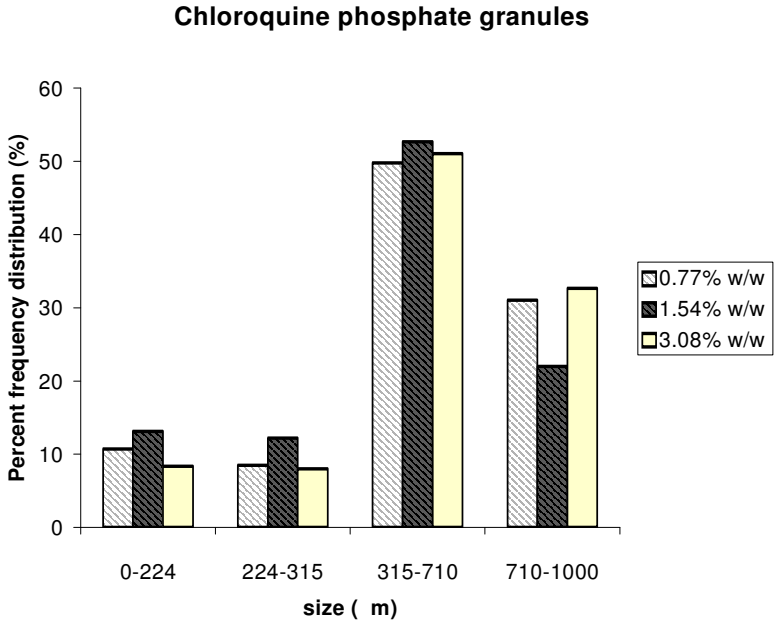


Figure 3.3 Percent frequency distribution by weight of (a) paracetamol granules and (b) chloroquine phosphate granules at different binder concentrations.

Table 3.6 Mean granule size (μm) of granules of paracetamol and chloroquine phosphate granules at different binder concentrations.

	Paracetamol				Chloroquine phosphate		
	Formula binder weight (% w/w)						
	1.35	2.7	5.4	8.1	0.77	1.54	3.08
Mean granule size	523	545	526	515	555	505	571

3.2.2 Determination of densities

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 higher bulk density require relatively lower die fill volume than those having small bulk density. As can be seen from Tables 3.7 and 3.8 the bulk and tapped density of the granules decreases with increasing concentration of binders. This could be attributed to the increase in the proportion of larger granules greater than 315μm with increasing the binder concentration. The granules occupied larger volume making the bulk density value lower than smaller granules occupying smaller bulk volume. Tables 3.7 and 3.8 also show that the granules of both substances (paracetamol and chloroquine phosphate) have Carr's compressibility index, calculated using equation (2.3), less than 15% implying the granules have excellent flow property. The Hausner ratio, calculated using equation (2.4), was also observed to be less than 1.25, which also confirmed that the granules have good flow property.

Table 3.7 Densities and related properties of paracetamol granules determined at different binder concentrations.

Formula binder weight (% w/w)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Compressibility index (%)	Hausner ratio
1.35	0.406 (0.003)	0.462 (0.009)	12.12	1.138
2.7	0.401(0.013)	0.456 (0.19)	12.06	1.137
5.4	0.373 (0.002)	0.427 (0.21)	12.72	1.145
8.1	0.36 (0.002)	0.413 (0.077)	12.83	1.147

Values in parenthesis indicate the standard deviation.

Table 3.8 Densities and related properties of chloroquine phosphate granules determined at different binder concentrations.

Formula binder weight (% w/w)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Compressibility index (%)	Hausner ratio
0.77	0.478 (2.09)	0.558 (2.54)	14.34	1.167
1.54	0.460 (0.88)	0.537 (0.707)	14.34	1.167
3.08	0.428 (0.567)	0.502 (0.707)	14.74	1.173

Values in parenthesis indicate the standard deviation.

3.2.3 Determination of granule flow rate

Measurement of granule flow rate is a direct method of determining granule flowability. The gum yielded granules with good flow properties as can be seen from Table 3.9. There was no significant difference in the angle of repose of the 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 same reason as the one given for bulk density, i.e., due to an increase in granule size. Moreover, greater flow was observed in the denser granulations. Higher flow rate was observed for chloroquine phosphate granules with binder concentration of 1.54% w/w. This increase in flow rate is probably due to the smaller granules mean size observed (Table 3.6 above).

3.2.4 Determination of friability

During a granule friability test, the granules may be reduced in size by attrition, i.e. removal of particle from the surface of the granule or by breakage or fragmentation of the whole granule. As expected, the friability of the granules of both substances was found to decrease with increased binder concentration, Table 3.10.

3.3 Calibration curve

The UV absorption calibration curve of paracetamol in phosphate buffer pH 5.8 at 243 nm over a concentration range of 0.002 – 0.012 mg/ml yielded a linear regression equation of: $Y = -0.00177 + 67.5X$ (where Y is the absorbance and X is the concentration in mg/ml) with narrow confidence interval and correlation coefficient of 1. Similarly, the UV absorption calibration curve of chloroquine phosphate in distilled water at 343 nm also yielded a regression equation of $Y = 0.00611 + 35.4X$ with correlation coefficients of 0.999 indicating that the sensitivity of the method was good.

Table 3.9 Flow rate and angle of repose of paracetamol and chloroquine phosphate granules measured at different binder concentrations.

	Paracetamol				Chloroquine phosphate		
	Formula binder weight (% w/w)						
	1.35	2.7	5.4	8.1	0.77	1.54	3.08
Flow rate (g/min)	172.4 (0.692)	167.32 (0.141)	164.2 (0.707)	187.5 (0)	168.5 (0.447)	182.8 (0.567)	164.2 (0.115)
Repose angle(^{0})	33.3 (0.223)	33.12 (0.346)	34.05 (0.247)	33.8 (0.459)	32.2 (0.092)	32.24 (0.629)	31.17 (0.261)

Values in parenthesis indicate the standard deviation.

Table 3.10 Friability of paracetamol and chloroquine phosphate granules determined at different binder concentrations.

	Paracetamol				Chloroquine phosphate		
	Formula binder weight (% w/w)						
	1.35	2.7	5.4	8.1	0.77	1.54	3.08
Friability (%)	3 (0.473)	2.35 (1)	2.1 (0.458)	2.6(1.28)	2.2(0.208)	1.8 (0.493)	1.3 (0.321)

Values in parenthesis indicate the standard deviation.

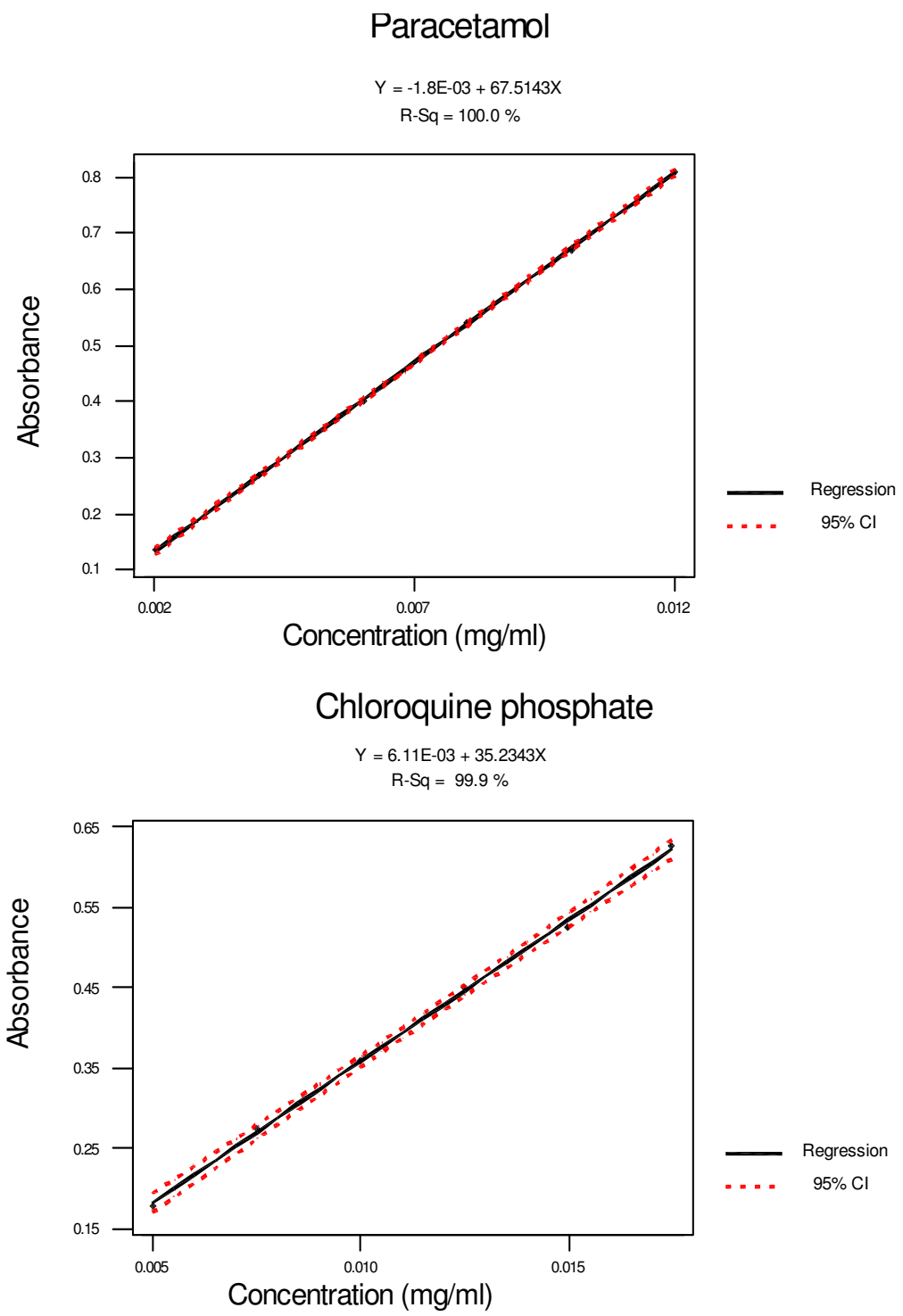


Figure 3.4 Calibration curves of Paracetamol and Chloroquine phosphate at 95% confidence interval.

3.4 Tablet compression

In order to cancel out the effect of disintegration on tablet dissolution, and also to decrease the particle size distribution, a fast acting disintegrant was used rather than starch. Ac-Di-Sol® is a super-disintegrant, which is made by a cross-linking reaction of Na-CMC. This cross-linking greatly reduced the water solubility of Na-CMC, while permitting the material to swell and absorb many times its weight in water without losing individual fibre integrity [107].

Ac-Di-Sol® added to tablet formulations at a high concentration, its absorption of water might cause an increase in viscosity of the liquid within the tablet, and further water penetration would be delayed and its disintegrant action would be reduced [107]. Therefore, 4% of Ac-Di-Sol® was used in the formulations.

Paracetamol tablets compressed using bevelled punches showed higher capping tendency than those compressed using the flat-faced punches (Tables 3.11a and 3.11b). This is because the surface of the bevelled tablets did not have equal time to relax during the decompression process. Consequently, the hardness and tensile strength of the tablets would be low and hence the tablets would have higher tendency to capping. Therefore, tablets compressed with flat-faced punches were selected and used for further analysis.

3.5 Tablet properties

Since the granules flow property was good, the tablet weights of both paracetamol and chloroquine phosphate were within the accepted range (± 5%). Tables 3.11a and 3.12 show that tablet thickness is related to, compression force and hardness. For all the binder concentrations used, increasing the compression force was found to decrease tablet thickness

when measured with the sliding calliper. This is because the die fill being constant, the increasing compression force would compress the particles more deeply decreasing tablet porosity and hence decreasing the tablet thickness. As a result a more compact and harder tablet resulted.

Table 3.11a. Summary of properties of paracetamol tablets with different binder concentrations and compressed using flat-faced punches at different compression forces.

Formula binder weight (%w/w)	Compression force (KN)*	Tablet thickness (mm)	Hardness (N)	Friability (%)	Disintegration time (min)	Tensile strength (kg/cm^2)
1.35	5	6.25 (0.02)	23.1(2.5)	8	0.6 (0.35)	2.35
	10	5.85 (0)	48.3(3.86)	3.2	0.73 (0.49)	5.26
	15	5.81 (0.04)	58.6(6.3)	Capping	0.73 (0.47)	6.42
2.7	5	6.35 (0)	29.6(4.6)	4.5	0.72 (0.35)	2.97
	10	5.95 (0)	61.3(3.83)	2	0.58 (0.49)	6.56
	15	5.8 (0.02)	85.1(5.8)	1	0.92 (0.7)	9.34
5.4	5	6.4 (0)	47.5(5.2)	2.6	1 (0.26)	4.72
	10	6.19 (0.02)	86.4(5.3)	1.8	3 (0.33)	8.89
	15	5.95 (0.02)	130(6)	1	10 (0.57)	13.9
8.1	5	6.2 (0)	72.1	1.69	8.58 (0.59)	7.4
	10	5.95 (0.026)	114 (8.06)	0.9	15.3 (1.25)	12.2
	15	5.7 (0.0176)	150 (21)	0.7	26.66 (2.36)	16.75

Values in parenthesis indicate the standard deviation.

* Capping occurred at compression force of 20 KN during the compression process, and therefore the tablets were omitted from further analysis.

Table 3.11b. Summary of properties of paracetamol tablets with different binder concentrations and compressed using bevelled punches at different compression forces.

Formula binder weight (%w/w)	Compression force (KN)	Weight (g)	Tablet thickness (mm)	Hardness (N)	Friability (%)
1.35 *					
2.7	5	0.54 (0.006)	6.35 (0.02)	26 (4.1)	4
	10	0.54 (0.004)	6.21 (0.02)	35.1 (4.07)	Capping
	15	0.53 (0.005)	5.9 (0.02)	50.5 (4.7)	Capping
5.4	5	0.53 (0.005)	6.4 (0.016)	34.2 (2.15)	1.5
	10	0.53 (0.004)	6.07 (0.03)	67.7 (5.3)	0.7
	15	0.54 (0)	5.95 (0.02)	69.9 (6.7)	Capping

* Tablets compressed at this binder concentration were not cohesive enough for further analysis. Therefore they were omitted.

Table 3.12 Summary of properties of chloroquine phosphate tablets with different binder concentrations and compressed at different compression forces.

Formula binder weight (%w/w)	Compression force (KN)	Tablet thickness (mm)	Hardness (N)	Friability (%)	Disintegration time (minutes)	Tensile strength (kg/cm^2)
0.77	10	5.55 (0.03)	56.7 (5.9)	1.8	3 (0.37)	6.5
	15	4.98 (0.12)	105.4 (4.99)	1.2	8 (0.33)	13.5
	20	4.76 (0.02)	130.7 (4.9)	0.99	11 (0.38)	17.5
	25	4.65 (0)	156.2 (5.5)	0.8	11.5 (0.59)	21.4
1.54	10	5.6 (0.03)	84.8 (4.2)	1.2	6 (0.71)	9.6
	15	5.45 (0)	118.8 (5.3)	1	10 (0.71)	13.9
	20	5.3 (0.03)	154.5 (7.3)	0.53	11 (0.52)	18.6
	25	5.4 (0.03)	177.5 (7.3)	0.51	13 (1.15)	20.9

Values in parenthesis indicate the standard deviation.

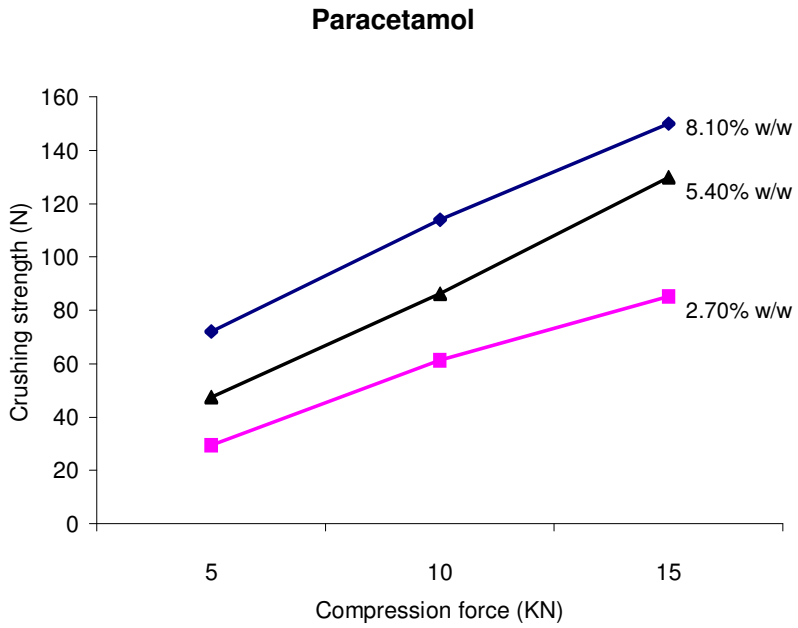
3.5.1 Tablet crushing strength and friability

As expected, for all the binder concentration used, increasing the compression force was found to increase the tablets' crushing strength of both substances and decrease the percent friability. This is clearly depicted in Figure 3.5. It can also be seen that increasing the binder concentration increased the tablets' crushing strength for the corresponding increase in compression force. The same relationship was found to percent friability (Figure 3.6). This can be explained by the fact that increasing binder concentration increases particle cohesiveness and results in harder tablets.

The higher friability values observed for paracetamol tablets compressed at lower compression forces could be due to the moisture content of the granules. Reports indicate that granules having optimum moisture content would result in tablets of less friable, less capping tendency and good hardness and tensile strength [104-108]. The lower hardness values observed for paracetamol tablets could also be attributed to the same problem mentioned for tablet friability. Tablet hardness may also affect the friability.

The paracetamol tablets were found to cap at higher compression force (above 15 KN). It is a known fact that hardness of a tablet is a function of the compressive force, the granule hardness and the ability to deform under load. Paracetamol is a poorly compressible drug with low degree of plastic flow and bonding, and therefore has a tendency to cap. Increasing the compression force made the problem worse and did not reduce friability. Moreover, the compression characteristics of paracetamol have been shown to be influenced by moisture content. Inter-particulate contact and hydrogen bonding of paracetamol particles and plastic deformation of the compressed tablets were enhanced by moisture level [31].

(a)



(b)

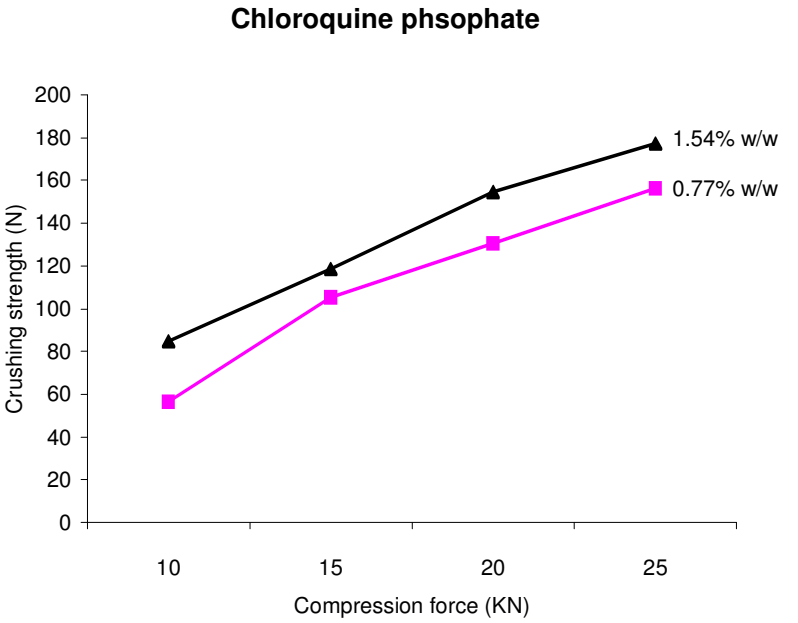
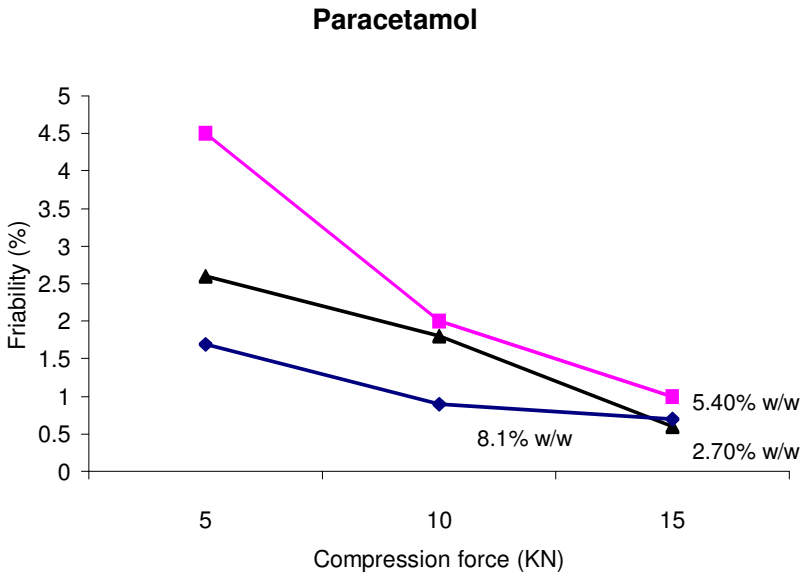


Figure 3.5 Relationships between compression force and crushing strength of (a) paracetamol tablets and (b) chloroquine phosphate tablets prepared with different binder concentrations.

(a)



(b)

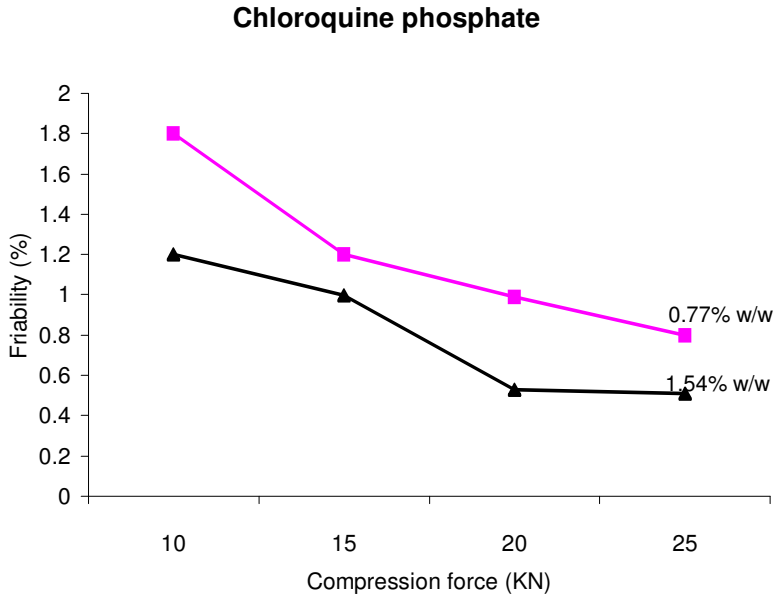


Figure 3.6 Relationships between compression force and friability of (a) paracetamol tablets and (b) chloroquine phosphate tablets prepared with different binder concentrations.

Tablet tensile strength is characteristics of internal friction or cohesion of the particles. Figure 3.7 shows that tablet tensile strength increases with increasing compression force. Tablet tensile strength is directly proportional to the crushing load (equation (1.4)). Therefore, increasing the compression force will lead to harder tablets, which need higher crushing load to break. Moreover, increasing binder concentration increased the tensile strength of the tablets for the corresponding increase in compression force.

The tensile strength of paracetamol tablets was lower than that of the chloroquine phosphate tablets. This lower tensile strength observed was probably due to the lower hardness of the tablets. The porosity of the paracetamol tablets was also higher than the chloroquine phosphate tablets, which might account for the lower tensile strength observed. It is reported that the tensile strength increases with less porous tablets [95].

3.5.2 Tablet porosity

The tablets of both substances were found to have lower porosity as the compression force increased. The porosity of the tablets also decreased as the binder concentration increased for the corresponding increase in compression forces as seen in tables 3.13 and 3.14. The porosity of chloroquine phosphate tablets was found to be lower than that of paracetamol tablets producing tablets with higher tensile strength. The tensile strength of the tablets increases with log of porosity.