# Evaluation of Binding Capacity of Gum Fraction of Local Myrrh (*Commiphora myrrha Syn. C.molmol*) in Granule and Tablet Formulations

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This is to certify that the thesis prepared by Taddese Mekonnen, entitled *Evaluation of Binding Capacity of Gum Fraction of Local Myrrh (Commiphora myrrha Syn. C.molmol) in Granule and Tablet Formulations* submitted in partial fulfillment of the requirements for the Degree of Master of Science in Pharmaceutics complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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# ABSTRACT

Evaluation of the Binding Capacity of the Gum Fraction of Local Myrrh (*Commiphora myrrha Syn. C.molmol*) in Granule and Tablet Formulations

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Addis Ababa University, 2012

Myrrh is an oleo-gum resin which is economically and culturally valuable product obtained from several species of the genus *Commiphora*. The chief source of myrrh is *Commiphora myrrha* (synonym *C. molmol*). They are important plant products used in several industries that include food, flavour, liquor and beverage, cosmetics, perfumery, pharmaceuticals and others.

Gums are considered to be pathological products formed following injury to the plant or owing to unfavorable conditions. They are frequently used in pharmaceuticals as thickening, binding, emulsifying, and suspending, gelling and stabilizing agents and also used as coating materials in microencapsulation. As binders they impart adhesive qualities to the powder material by formulation of granules of the desired size, hardness, strength, friability and compressibility.

In this study, the gum fraction of myrrh oleo-gum resin was extracted from local myrrh (*Commiphora myrrha* syn. *C. molmol*) and its binding capacity in granule and tablet formulations was evaluated using paracetamol as a model drug. Some physico-chemical properties of the extracted gum such as the presence of tannin and starch/dextrin, loss on drying, total ash value, pH of gum mucilage, water solubility index, swelling power, relative solubility, moisture sorption-desorption, viscosity and powder flow properties were investigated. Granules containing paracetamol were prepared using 2%, 5%, 7.5% and 10% w/w of the extracted gum and reference binders (PVP K-30 and Acacia BP) by wet granulation technique. The granules were characterized for particle size and size distribution, bulk and tapped densities, compressibility index and Hausner ratio, angle of repose, flow rate and friability. Tablets containing paracetamol and different concentrations of binders were prepared using a single punch tablet machine at a fixed compression force. Tablets were evaluated for their weight uniformity, thickness,

diameter, hardness (crushing strength), tensile strength, friability, disintegration time and *in vitro* release profile. Finally, some properties of granules and tablets prepared with the extracted gum were compared with properties of respective granules and tablets prepared using the reference binders.

The results indicated that the myrrh gum exhibited good relative solubility in cold and hot water, good water solubility index, poor swelling power, acceptable moisture content, small total ash value, no tannin and starch/dextrin content, gum mucilage with acidic pH, high moisture sorption-desorption pattern, and acceptable viscosity and powder flow properties. The granules prepared with the myrrh gum and reference binders all showed good particle size and size distribution, flow and compressibility properties, and friability decreased with increasing binder concentration.

All the prepared tablets passed pharmacopoeial specifications with respect to their uniformity of weight, thickness, diameter, hardness and tensile strength. However, all tablets with 2% binder concentration failed to comply with the pharmacopoeial specification for friability test (> 1%). Disintegration times of tablets were determined and only those tablets prepared with myrrh gum and acacia as binders at 10% concentrations failed to meet the British pharmacopoeia specification for disintegration (>15 min). *In vitro* drug release studies showed that there was a general decrease in the release rate of paracetamol from the tablets as the binder concentration increased. Tablets made with myrrh gum as binder gave higher dissolution profile than acacia and comparable profile to tablets prepared with PVP K-30.

***Key Word***: Myrrh gum

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# ACRONYMS

| | |
|---|---|
| API: | Active pharmaceutical ingredient |
| BP: | British Pharmacopoeia |
| FTIR: | Fourier transform-infrared |
| RPM: | Revolution per minute |
| SD: | Standard deviation |
| TS: | Test solution |
| USP: | United State Pharmacopoeia |
| UV: | Ultra violet |

# 1. INTRODUCTION

## 1.1 Myrrh

Myrrh is an oleo-gum-resin obtained from several species of the genus *Commiphora*, a member of the *Burseraceae* family. It is pale yellow colour, changing to dark red upon hardening (Vollesen, 1989).

**Figure 1.1 Photo of oleo-gum-resin of myrrh (picture taken by Mekonnen T.).**

### 1.1.1 The phytochemistry of myrrh

Myrrh consists of water-soluble gum (40 - 60%), alcohol-soluble resins (23 - 40%), volatile oils (2 - 8%) and a bitter principle (10 - 25%); it has a characteristic odour ascribed to the presence of furanosesquiterpenes (El-Ashry *et al*., 2003).

The water-soluble gum or mucilage fraction is composed mainly of acidic polysaccharide with galactose, xylose, 4-0-methyl-glucuronic acid and arabinose in a ratio of 8: 7: 2 with 18–20% protein and also on hydrolysis the gum yields arabinose, galactose, xylose and 4-0-mythylglucuronic acid (Lemenih and Teketay, 2003).

The alcohol-soluble resins of myrrh consist of α, β-, and γ-commiphoric acids, commiphorinic acid, α and β-herrabomyyhols, heerboresene, commiferin, kertosteroids, compesterol, β-sitosterol, cholestrerol, α- amyrone and 3-epi-α-amyrin. The volatile oil contains terpenes, sesquiterpenes, esters, elemol, cinnamaldehyde, cuminaldehyde,

cumicalcohol, eugenol, heerabolene, limonine, dipentene, pinene, m-cresol, cadinene and numereous furanosesquiterpenes (Rao *et al.*, 2001).

### 1.1.2 Myrrh production and collection

Myrrh production is carried out by collecting exudates from trees in natural stands by random picking from naturally and/or accidentally exuding trees by peasants and pastoralists. This collection is considered secondary as it is carried out while executing other activities perceived to be more important namely firewood collection and livestock (Tadesse *et al*., 2007).

### 1.1.3 Uses of myrrh

Frankincense and myrrh have wide-ranges of industrial uses in areas such as food industry, beverages, candies, chewing gums, confectioneries, gelatins, nut products, puddings and canned vegetables. They are also used in folk medicines, flavoring, beverages and liquors, cosmetics, detergents, creams and perfumery, paints, adhesives and dyes manufacturing (Tilahun, 1997; Getachew and Wubalem, 2004).

They are highly valued for their aromatic fragrances and are common ingredients in incense, perfume and potpourris, soaps, detergents, creams and lotions, and are often included in meditation blends, as it strengthens the psyche and aids in deepening the meditative state. Typical applications include: adhesive thickeners, thickeners, stabilizers, flavouring, fixatives and emulsifying agents in food products, clarification in beverages, and release agents for rubber products (FAO, 1995).

### 1.1.4 Biological and toxicological properties

Frankincense and myrrh are phytotoxically safe raw materials in industries like pharmaceuticals and food. Myrrh, like many herbal and botanical products, is safe to humans. This natural flavoring substance has been approved by the U.S. FDA (Ford *et al*., 1992; FAO, 1995).

In acute toxicity test report in mice, *C. molmol* exhibited no visible signs of toxicity and no mortality was observed up to 3 g/kg dose level. However, some decrease in locomotor activity at a dose of 3 g/kg was noticed, which may be attributed to the presence of high

contents of volatile oils in *C. molmol*. In general, volatile oils are known to have depressant action on the central nervous system (Ahmad *et al*., 1993).

There were no toxicity symptoms upon chronic treatment of mice with *C. molmol*. During 0 to 30 days, one male and one female mice died in the control group while in *C. molmol* treatment group, no animal died. All the treated male and female mice throughout the study were normal and comparable to the control (Rao *et al*., 2001).

### 1.2 Gums

Gums are considered to be pathological products formed following injury to the plant or owing to unfavorable conditions, such as drought, by a breakdown of cell walls (extracellular formation; gummosis). They are present in high quantities in varieties of plants, animals, seaweeds, fungi and other microbial sources, where they perform a number of structural and metabolic functions. Plant sources provide the largest amount of gums. Acacia, tragacanth, and guar gum are examples of gums (Jani *et al*., 2009; Ofori-kwakye *et al*., 2010).

Plant gums are hydrocolloids. They are also translucent amorphous substances and polymers of a monosaccharide or mixed monosaccharides and many of them are combined with uronic acids. Gums, on hydrolysis, yield a mixture of sugars and uronic acids. They contain hydrophilic molecules, which can combine with water to form viscous solutions or gels (Jani *et al*., 2009).

Plant gums have been widely used in various industries like paper, textile, food, pharmaceuticals, ink, cosmetics and petroleum due to their abundance in nature and low cost. They are frequently used in pharmaceuticals as thickening, binding, emulsifying, suspending, gelling and stabilizing agents and also used as coating materials in microencapsulation. As binders, they impart adhesive qualities to the powder material by formulation of granules of the desired size, hardness, strength, friability and compressibility (Girhepunje *et al*., 2009).

### 1.3 Gum and resin bearing species in Ethiopia

Ethiopia is one of the countries well endowed with various species of *Acacia*, *Boswellia* and *Commiphora* that are known to produce gum arabic, frankincense and myrrh, respectively. Available estimates indicate that the total area of oleo-gum resin bearing woodlands cover about 2.9 million hectares of land in the country (Table 1.1), with over 300,000 metric tons of natural gum production potential (Girmay, 2000). The trees produce resin in the dry season and provide people with meaningful economic activities in a period with few other economic alternatives (Lemenih *et al*., 2003).

Table 1.1 Estimated areas covered by natural gum and resin bearing species in the different regions of Ethiopia.

| Regional State | Genus | Estimated area (ha) |
|---|---|---|
| Tigray | *Boswellia, Sterculia, Commiphora* & *Acacia* | 940,000 |
| Amhara | *Boswellia,Commiphora, Acacia* & *Sterculia* | 680,000 |
| Oromia | *Boswellia, Acacia, Commiphora* & *Sterculia* | 430,000 |
| Gambella | *Sterculia, Acacia* & *Commiphora* | 420,000 |
| Somali | *Boswellia, Acacia* & *Sterculia* | 150,000 |
| Benshangul-Gumuz | *Boswellia, Acacia* & *Sterculia* | 100,000 |
| SNNP | *Boswellia, Acacia* & *Sterculia* | 70,000 |
| Afar | *Commiphora* & *Acacia* | 65,000 |
| Total | | 2,855,000 |

*Source:* Girmay, 2000 *SNNP: Southern Nations, Nationalities and Peoples*

Over 60 gum and resin bearing species are found in the country (Tadesse *et al*., 2007). The most commonly well known sources of gum and resin species in Ethiopia are listed in Table 1.2.

Table 1.2 List of common gum and resin bearing trees and shrubs in Ethiopia by genus and species.

| No | Genus *Commiphora* | No | Genus *Boswellia* |
|---|---|---|---|
| 1 | *Commiphora myrrha* Syn. C. *molmol* | 1 | *Boswellia papyrifera* |
| 2 | *Commiphora Africana* | 2 | *Boswellia microphylla* |
| 3 | *Commiphora habessinica* | 3 | *Boswellia neglecta* |
| 4 | *Commiphora truncata* | 4 | *Boswellia ogadensis* |
| 5 | *Commiphora boranensis* | 5 | *Boswellia pirrotae* |
| 6 | *Commiphora guidottii* | 6 | *Boswellia rivae* |
| 7 | *Commiphora schimperi* | | **Genus *Acacia*** |
| 8 | *Commiphora erythraea* | 1 | *Acacia Senegal* |
| 9 | *Commiphora corrugata* | 2 | *Acacia seyal* |
| 10 | *Commiphora cyclophylla* | 3 | *Acacia polyacantha* |
| 11 | *Commiphora hildebrandtii* | 4 | *Acacia sieberiana* |
| 12 | *Commiphora odia* | 5 | *Acacia drepanolobium* |
| 13 | *Commiphora kua* | | |
| 14 | *Commiphora serrulata* | | |
| 15 | *Commiphora monoica* | | |

*Source:* Tadesse *et al*., 2007

### 1.4 Genus *Commiphora*

The name *Commiphora* originates from the Greek words *kommi* (meaning 'gum') and *phero* (meaning 'to bear'). The majority of the species yield a fragrant oleo-gum-resin (Steyn, 2003). *Commiphora* has shown to dominate over 1.6 million $km^2$ of *Acacia-Commiphora* woodland in (sub-) tropical East Africa (Weeks and Simpson, 2006).

Although the common name for *Commiphora* species is 'corkwood' (an indication of the softness of the wood), it is suitable for use as fences, as well as for carving utensils and

other ornaments. The Afrikaans name for *Commiphora* is 'kanniedood', the direct translation being 'cannot die'. This is an indication of the sustainability of the plant and also refers to the fact that the truncheons grow easily when planted. Yellowing and shedding of the leaves occurs early in autumn, and the plants are deciduous for most of the year, a feature very typical of *Commiphora.* Aspects of the life history of the species include a deciduous habit, a predominantly dioecious breeding system and a tendency to produce flowers prior to developing leaves (Weeks and Simpson, 2006).

The Genus *Commiphora* includes 150-200 species widespread in the drier parts of tropical Africa and Madagascar. The genus is a very conspicuous and dominant element in the dry bush lands of Northeast Africa, and a large number of species are endemic in this area (Vollesen, 1989).

Fifty-two species of *Commiphora* are known to exist in Ethiopia, and 14 (about 25%) of the species are endemic. However, very few are used to collect resin (Table 1.2). The chief *Commiphora* gum of highly economic importance is myrrh (Fig. 1.1), produced by *Commiphora myrrha* (Nees) Engl. (1883), *(*synonym *C. molmol)*. This is an important commodity of commerce in Southern and South Eastern Ethiopia (Vollesen, 1989).

### 1.5 *Commiphora myrrha*

*Commiphora myrrha* is a member of *Burseraceae* family. It is an indigenous tree or shrub that grow to about 3 m in height; bark silvery or whitish to bluish grey, peeling in small to large papery flakes, sometimes reticulately fissured on old trunks; all parts glabrous. It grows in *Acacia-Commiphora* woodland and bush land on sandy to loamy soil overlying limestone or granite, rocky lava hills; 250-1,300 m. It is widely distributed in Afar, Sidama, Bale, Hararge regions of Ethiopia and in Somalia, North East Kenya and Arabia (Vollesen, 1989).

In biblical times, *Commiphora myrrha* (Fig.1.2) was valued as much as gold, and is mentioned numerous times in the Old Testament, in instructions to Moses about making incense and anointing oil, for which it has been used throughout history. Also of great religious importance, it was presented as one of the three gifts to Christ by the Magi, and was used to anoint the body of Christ after the crucifixion (Dharmananda, 2003).

Figure 1.2 *Commiphora myrrha*, a thorny shrub or small tree about 3 m in height.

*Source:* **http://www.naturesessences.com.**

### 1.6 Pharmaceutical excipients

Pharmaceutical excipients are additives used to convert the active pharmaceutical ingredients into dosage forms suitable for administration to patients. They are components of dosage forms that enable the formulations to acquire some characteristics which will establish the basic features of the formulated product. These excipients control physicochemical properties as well as the release profiles and availability of the drug in the system (Mahmud *et al*., 2008).

The physicochemical properties of a compound are measurable characteristics by which the compound may interact with other systems. The ability of excipients to provide their intended function and perform throughout the shelf life of the product must be established such that the information will justify the choice, concentration and characteristics that may influence the final product (Mahmud *et al*., 2008).

One of the commonly used groups of compounds as excipients is natural polymers. They are composed of a large group of polymers with varying chemical compositions, large derivitizable groups and a wide range of molecular weights. They are characterized by

low toxicity, high stability and biodegradability. These properties make them appealing as pharmaceutical excipients (Anekant *et al*., 2007).

Plant products as excipients are attractive alternatives to synthetic products because of their biocompatibility, low toxicity, environmental "friendliness" and low price. Natural gums, polymers obtained commonly from plants, have diverse applications in drug delivery as disintegrant, emulsifying, suspending agents and as binders. They have also been found useful in formulating immediate and sustained release preparations (Singh *et al*., 2010).

### 1.6.1 Binders

Pharmaceutical tablets must have the mechanical strength to withstand the rigors of handling involved in manufacturing, packaging, transportation, dispensing, and in the hands of the user. They must also, in relevant cases, be able to release the drug content in the gastrointestinal tract for absorption. The mechanical strength of tablets is quantifiable by their crushing strength and friability, whereas their release properties are quantifiable by their disintegration and dissolution profiles (Banker and Anderson, 1996). These parameters in turn have been shown to depend considerably on the nature and concentration of the binding agent used in tablet formulation (Itiola and Pilpel, 1996).

Binders are employed in pharmaceutical tablet formulation to provide adequate mechanical properties by promoting the bonding properties existing between the different components of a powder mixture in a formulation. Various natural, semi-synthetic and/or synthetic substances like starches, cellulose and gums have been employed in pharmaceutical tablet formulation as binders. Gums are examples of hydrophilic substances employed in pharmaceutical solid dosage formulation mainly as binders (Adetogun and Alebiowu, 2009).

## 1.7 The present study

The traditional use of excipients in drug formulations was to act as inert vehicles to provide necessary weight, consistency and volume for the correct administration of the active ingredient, but in modern pharmaceutical dosage forms they often fulfill multi-functional roles such as modifying release, improvement of the stability and bioavailability of the active ingredient, enhancement of patient acceptability and ensure ease of manufacture. New and improved excipients continue to be developed to meet these needs of advanced drug delivery systems (Raymond *et al.*, 2006; Patel *et al*., 2007).

A large number of plant-based pharmaceutical excipients are available today. Many researchers have explored the usefulness of plant-based materials as pharmaceutical excipients. Ability to produce a wide range of material based on their properties and molecular weight, natural polymers became a thrust area in majority of investigations in drug delivery systems. Gums are one of these natural polymers used as excipients mainly as binders. Besides, they can also be modified to meet the requirements of drug delivery systems and thus can compete with the synthetic excipients available in the market (Banker and Anderson, 1996; Bhardwaj *et al*., 2000).

A number of binding agents are available for use in tablet formulations. However, different binding agents can be useful in achieving various tablet mechanical strength and drug release properties for different pharmaceutical purposes. Thus, the development of new excipients for potential use as tablet binders continues to be of interest (Odeku and Itiola, 2003).

Recently, Kumar and Singh investigated the potential of myrrh oleo-gum resin (MOGR) as a directly compressible tablet excipient, primarily as a binder and release retardant using Tramadol as a model drug. The result suggested that myrrh oleo-gum resin could be positively explored for its binding and release retardant property in various drugs (Kumar and Singh, 2010).

In the present work, the gum portion of myrrh from *Commiphora myrrha syn. C.molmol* was isolated, purified and characterized for its suitability as a binding agent in granules and tablet formulations using paracetamol as a model drug. Paracetamol is a sparingly

soluble drug with poor compression properties, which requires a binding agent among other excipients to form satisfactorily strong tablets (Odeku and Itiola, 2003). The effects of the gum portion of myrrh on granules and on the mechanical properties, friability and the disintegration and dissolution characteristics of paracetamol tablets were investigated, in comparison with two reference binders.

## 1.8 Objectives of the study

### 1.8.1 General objective

- To evaluate the binding capacity of the gum fraction of local myrrh (*Commiphora myrrha* syn. *C. molmol*) in granule and tablet formulations.

### 1.8.2 Specific objectives

- To extract, purify, characterize the gum fraction of myrrh for solubility, pH, viscosity, swelling ratio, mass loss on drying, ash value, percentage yield, moisture sorption-desorption pattern, test for tannin and starch/dextrin;
- To prepare granules using different proportions of gum fraction of myrrh and reference binders (Acacia and PVP K-30) and determine their physical properties (size, size distribution, bulk density, tapped density, compressibility index, Hausner's ratio, granule friability and flowability);
- To prepare compressed tablets of paracetamol containing different proportions of gum fraction of myrrh and reference binders; and to determine properties of the compressed tablets namely; weight uniformity, hardness (crushing strength), tensile strength, friability, disintegration time, paracetamol estimation and *in vitro* drug release profile and
- To compare some properties of tablets prepared with gum fraction of myrrh as a binder with two reference binders.

# 2. EXPERIMENTAL

## 2.1 Reagents

Iodine and ferric chloride test solutions were prepared according to USP (USP/NF, 30, 2007). Accordingly, 14 g of iodine was added to 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 test solution was prepared by dissolving 9 g of ferric chloride in water to make 100 ml.

## 2.2 Materials

Oleo-gum resin of local myrrh (*Commiphora myrrha syn. C. molmol*, one year old, from Liban woreda) was obtained from the Natural Gum Processing and Marketing Enterprise of Ethiopia. Paracetamol reference standard (batch no.0740286, Paracetamol micronized working sample, Horst), Paracetamol powder BP (batch no. 1110531, China Associate Co. Ltd, China) and corn starch were obtained from Ethiopian Pharmaceutical Manufacturing (EPHARM), Addis Ababa. Lactose (BDH chemicals Ltd., Poole England) and PVP K-30 (KOJE Polymers) were obtained from Cadila Pharmaceuticals Factory, Addis Ababa. Acacia (BDH chemicals Ltd., Poole, England), Talc (BDH chemicals Ltd., Poole England), Magnesium stearate (BDH chemicals Ltd., Poole England), chloroform, alcohol, and acetone were used as received.

## 2.3 Methods

### 2.3.1 Preparation of myrrh oleo-gum resin

The myrrh oleo-gum resin obtained was dried in oven (Kottermann® 2711, Germany) at 60 °C for 24 hours, powdered in a blender and passed through sieve with a mesh size of 224 µm.

### 2.3.2 Gum extraction and purification

In order to extract the gum portion from the oleo-gum resin, 100 g of the powder was stirred with 500 ml of ethanol 90% v/v for 2 h. The ethanolic slurry was filtered through Whatman No.1 filter paper. The residue was washed with 100 ml of ethanol 90% v/v

twice and then the residue was dried at 40°C for 12 h in an oven (Kottermann® 2711, Germany). After drying, the extracted powder was dissolved in 500 ml distilled water at room temperature and then filtered through a muslin cloth. Thereafter, the gum was precipitated from the slurry using ethanol (90% v/v) in 1:2 ratios, filtered through a muslin cloth and the precipitate was dried in an oven at 40 °C for 48 h. The dried flakes were pulverized using a blender to fine particles, sieved through a 224 µm sieve and stored in an air tight container. Percentage yield of the pure gum was determined using equation 2.1 (Milani *et al*., 2007; Mahmud *et al*., 2008).

$$Percentage\ yield = \frac{\text{Pure gum(g)} \quad \text{x } 100}{100\text{(g)}} \tag{2.1}$$

### 2.3.3 Physicochemical characterization of the myrrh gum

#### 2.3.3.1 Presence of starch or dextrin

10 ml solution of the gum (10% w/v) was boiled and cooled and 0.1 ml iodine TS was added to check for presence of starch or dextrin in the gum (BP, 2009).

#### 2.3.3.2 Test for tannin bearing gums

0.1 ml of ferric chloride TS was added to 10 ml (10% w/v) of gum solution to check for the presence of tannins in the gum (BP, 2009).

#### 2.3.3.3 Relative solubility

The relative solubility of the gum was determined in cold and hot distilled water, acetone, chloroform and ethanol employing the method used by Mahmud *et al.* (2008). Accordingly, 1 g myrrh gum powder was added to 10 ml of each of the above mentioned solvents and left overnight. Five ml of the clear supernatants was taken in small pre-weighed evaporating dishes and heated to dryness over a digital thermostatic water bath at 50 °C for organic solvents and at 105 °C for distilled water for 2 h. The weights of the dried residue with reference to the volume of the solutions were determined using a digital balance and expressed as the percentage solubility of the gum in the solvents.

### 2.3.3.4 Water solubility index and swelling power

Water solubility index and swelling power of the gum were determined according to the methods described elsewhere. Firstly, 0.5 g gum powder was weighed directly into pre-weighed centrifuge tubes, and 10 ml of distilled water was added to each tube. The tubes were then kept in a thermostatically controlled water bath at 25 $^{o}$ C for 30 min with frequent mixing at 2 min intervals. The tubes were then cooled centrifuged at 3000 rpm for 15 min. The supernatant was removed and the sediment weight (Ws) was determined. The supernatant was dried to constant weight (W1) in an oven (Kottermann® 2711, Germany) at 105 $^{o}$ C for 12 hrs. The water solubility index (WSI) and swelling power (SP) of the gum were calculated using equations 2.2 and 2.3, respectively (Torruco-Uco and Betancur-Ancona, 2007).

$$WSI = \frac{W1 \ x\,100\%}{0.5} \tag{2.2}$$

$$SP = \frac{Ws\,x\,100}{0.5(100 - WSI)} \tag{2.3}$$

### 2.3.3.5 Viscosity of gum mucilages

A rotational viscometer (KINEMATICA, AG, Type Viscosta + L, Switzerland) was used for this study. Different concentrations (2.0, 5.0, 7.5 and 10% w/v) mucilages of myrrh gum, PVP K-30 and acacia samples were prepared in a 600 ml beaker, appropriate enough to immerse the spindle groove in the fluid and viscosity was measured using spindle number 1 at a shear rate of 200 rpm. For each concentration, triplicate measurements were made.

### 2.3.3.6 Determination of the pH of gum mucilage

The pH of the gum mucilage (5% w/v) was determined using a Wagtech pH meter (Model 3510). The pH meter was set to neutral at a room temperature of 28 °C and the electrode was immersed into the mucilage. The reading on the meter was recorded. Triplicate measurements were made.

### 2.3.3.7 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 30 g of the gum powder. The content was allowed to pour out and the time taken for the powder to flow through the orifice was recorded. The flow rate and angle of repose were calculated using the formulas below and the values were averages of three determinations.

$$Angle\ of\ repose\ (\Theta) = tan^{-1}\left(\frac{h}{r}\right) \tag{2.4}$$

$$Flow\ rate\ (g/sec) = \frac{\text{Weight of powder}}{\text{Time}} \tag{2.5}$$

where, h is the height of the powder pile and r is the radius of the pile.

### 2.3.3.8 Loss on drying

The method adopted was a modification of that specified in the British Pharmacopoiea (B.P., 2009) for acacia. A 1.0 g quantity of the sample was transferred into a petri dish and then dried in an oven at 105 °C until a constant weight was obtained. The percent moisture content was then determined as the ratio of the weight of moisture lost to weight of sample multiplied by 100.

### 2.3.3.9 Total ash determination

Ash values of the samples were determined based on the method in the B.P. ( 2009). A 1 g sample of powder was weighed in a pre-weighed ashing crucible followed by heating in a furnace (Naber Industrieofenbau, Bremen, Germany) at 450 $^{o}$C for 8 h. The sample was then removed and kept in a desiccator and weighed. Total ash values in the samples of interest were calculated using Equation 2.6.

$$Total\ ash\ (\%) = \frac{m_2 - m_1}{m} x100 \quad (2.6)$$

where, $m_1$ is mass of the ashing crucible, $m_2$ is mass of crucible plus ash and $m$ is mass of sample.

#### 2.3.3.10 Moisture sorption-desorption studies

The method described by Josiah (1991) was adopted. A dried evaporating dish was weighed and 2 g of the gum powder were weighed into it. The final weight of the dish was noted and then placed over water in a desiccator for a period of 5 days, thereafter removed and transferred into another desiccator over activated silica gel (desiccant) for another 5 days. The dish with its content was weighed on daily basis and its moisture content was calculated in triplicate.

#### 2.3.3.11 Determination of bulk and tapped densities

Thirty grams of the gum powder were carefully introduced into 250 ml measuring cylinder, the volume occupied by the powder was read to the nearest 0.5 ml and the bulk density ( $\rho_B$ ) was calculated as g/ml. The bulk densities were determined using Equation 2.7.

$$Bulk\ density\left(\rho_B\right) = \frac{m}{V_B} \quad (2.7)$$

where, $m$ is mass of sample (in g) and $V_B$ is the bulk volume of sample powder.

The bulk in the cylinder was tapped using tapped densitometer (ERWEKA, SVM 20, Germany), which provides a fixed drop of one-half inch at a rate of 250 taps/min for -- min. The volume occupied by the gum powder was recorded and the tapped densities ( $\rho_T$ ) were determined using Equation 2.8. The bulk and tapped densities recorded were averages of three determinations.

$$Tapped\ density\left(\rho_T\right) = \frac{m}{V_T} \quad (2.8)$$

where, $m$ is mass of sample and $V_T$ is tapped volume of the sample.

#### 2.3.3.12 Density related properties

Hausner ratio and Carr's index (percent compressibility) which are used to determine the flow and compressibility properties of powder, respectively, were calculated from bulk and tapped densities using Equations 2.9 and 2.10.

$$Carr's\ index\ (\%) = \left( \frac{\rho_T - \rho_B}{\rho_T} \right) X 100 \tag{2.9}$$

$$Hausner\ Ratio = \left( \frac{\rho_T}{\rho_B} \right) \tag{2.10}$$

#### 2.3.3.13 Fourier transformed-infrared (FTIR) study

To study the gum and drug interaction, the pure gum, a mixture of the gum and the drug and the drug without the gum were mixed separately with IR grade KBr disk in the ratio 100:1 using paraffin as a film forming agent. The well-ground and mixed powdered samples were compressed in to KBr disk by applying a pressure in a hydraulic press and the films on the disk were scanned over a wave number of 4000-400 $cm^{-1}$ in an IR spectrometer (SHIMADZU, FTIR-8400S, Japan). The major peaks of IR spectra of paracetamol in the mixture were analyzed and compared with respect to the IR spectra of paracetamol alone.

### 2.3.4 Preparation of granules

The different batches of paracetamol granules F1–F12 (100 g) were prepared using different concentrations (2, 5, 7.5 and 10% w/w) each of myrrh gum, PVP K-30 and acacia as binders using the wet granulation technique using the quantities in Table 2.1. Acacia and PVP K-30 were used as standard binders for comparison purpose. The desired quantities of paracetamol and lactose were dry mixed for 5 min using a Turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland). The mixture was moistened with the exact amount of wet granulating fluid to produce granules containing various concentrations of binders. Massing continued for 5 min, the wet masses were granulated manually by passing through a 1600 μm sieve, dried in a hot air oven for 18 h at 50 °C.

Dried granules were passed through a 1000 μm sieve and then stored in air-tight containers.

### 2.3.5 Characterization of granules

#### 2.3.5.1 Particle size and size distribution of granules

Thirty grams of granules from each batch were put in a set of sieves (ISO 3310-1) fixed on a universal drive unit (ERWEKA, Type AR 401, Germany) arranged in mesh size from top to bottom with the widest sieve on the top. Then, the sieves were shaken for 2 min. The granules remaining on each sieve were weighed and percent granules retained on each sieve were recorded and mean granule size was calculated for each batch. 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.

#### 2.3.5.2 Determination of bulk and tapped densities

The bulk and tapped densities of granules were calculated using equation 2.7 and 2.8 in section 2.3.3.11.

#### 2.3.5.3 Density related properties

Hausner ratio and Carr's compressibility index of the granules were obtained using equations 2.9 and 2.10 in section 2.3.3.12.

#### 2.3.5.4 Determination of granule flow rate and angle of repose

The flow rate and angle of repose of granules were calculated using equations 2.5 and 2.4 in section 2.3.3.7. Granule flow rates and angle of repose values were averages of five determinations.

#### 2.3.5.5 Determination of granule friability

Ten grams of each batch of granule larger than 315 μm were put in Erweka Friabilator (ERWEKA type TAR-20, Germany) and allowed to revolve for 4 min at 25 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 were averages of four determinations.

### 2.3.6 Preparation of paracetamol tablets

Corn starch, talc and magnesium stearate were passed through a 224 μm sieve, added together onto dry granules (Table 2.1) and blended for 5 min in a Turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland) at 49 rpm. The granules were compressed into tablets at a fixed compression force on eccentric tablet machine (EK0 Korsch, 8410-68, Berlin, Germany) which was fitted with 10 mm diameter flat-faced punches. The die volume corresponds to the weight of the tablet to ensure that 420 mg paracetamol tablet was obtained. The tablets were kept for 24 h at room temperature in glass containers before their properties were evaluated.

Table 2.1 Composition of the different batches of paracetamol tablets prepared with myrrh gum, PVP K-30 and acacia as binders.

| Ingredients | Batch code | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
| Paracetamol | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |
| Myrrh gum | 8.4 | 21 | 31.5 | 42 | - | - | - | - | - | - | - | - |
| PVP K-30 | - | - | - | - | 8.4 | 21 | 31.5 | 42 | - | - | - | - |
| Acacia | - | - | - | - | - | - | - | - | 8.4 | 21 | 31.5 | 42 |
| Lactose | 63.4 | 50.82 | 40.32 | 29.82 | 63.42 | 50.82 | 40.32 | 29.82 | 63.42 | 50.82 | 40.32 | 29.82 |
| Corn starch | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 | 42 |
| Mg stearate | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 | 4.2 |
| Talc | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 | 2.1 |
| Total (mg/tablet) | 420 | 420 | 420 | 420 | 420 | 420 | 420 | 420 | 420 | 420 | 420 | 420 |

### 2.3.6 Evaluation of paracetamol tablets

Compendial and non-compendial tests were undertaken to assess the quality and performance of myrrh gum in comparison with the standard binders. These tests include weight uniformity, hardness (crushing strength), tensile strength, friability, disintegration time, paracetamol estimation and *in vitro* drug release profile.

#### 2.3.6.1 Weight and thickness of tablets

Twenty tablets were randomly selected from each batch and assessed gravimetrically on an individual basis using an analytical balance (Mettler Toledo, PR 203, Switzerland). The mean weight as well as standard deviation were calculated. The thicknesses of the tablets were measured using sliding caliper scale (Nippon Sokutei, Japan).

#### 2.3.6.2 Crushing strength

The load required to break the tablet (crushing strength) at room temperature into two equal halves was determined by the application of a diametrical force using a hardness tester (Schleuniger, 2E/205, Switzerland). The results were expressed as the mean of three determinations.

#### 2.3.6.3 Tensile strength

The tensile strengths (*T*) of the normal tablets were determined at room temperature by diametrical compression using a Schleuniger hardness tester (Schleuniger, 2E/205, Switzerland) and by applying the equation:

$$T = 2F/\pi dt \qquad (2.11)$$

where, *T* is the tensile strength of the tablet ($kgxcm^2$), *F* is the load (MN) needed to cause fracture, *d* is the tablet diameter (m) and *t* is the thickness (m). All results were expressed as the mean of triplicate determinations.

#### 2.3.6.4 Friability testing

To evaluate the friability of the tablets from each batch, ten intact tablets were randomly selected, dedusted and weighed. The tablets were then placed in an Erweka Friabilator (ERWEKA type TAR-20, Germany) and subjected to its tumbling actions at 25 rpm for 4 min. Afterwards, the tablets were once again dedusted and reweighed to determine the percentage loss of weight.

#### 2.3.6.5 Disintegration tests

Six tablets from each batch were tested for disintegration times in distilled water at 37 ± 2 °C using a Disintegration Apparatus (CALEVA, G.B. Caleva Ltd., UK) USP,NF 27/30. The disintegration time was taken to be the time at which no granule of any tablet was left on the meshes of the apparatus.

#### 2.3.6.6 Estimation of paracetamol

Paracetamol content of the tablets was estimated by UV spectrophotometric method based on the measurement of absorbance. Stock solution containing 0.2 mg/ml of paracetamol in phosphate buffer of pH 5.8 was prepared and diluted to six different concentrations (0.002, 0.004, 0.006, 0.008, 0.01, 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 were calculated (USP 30/NF 25, 2007).

#### 2.3.6.7 *In vitro* drug release studies

The release profile of paracetamol from tablets was determined using USP 30/25 dissolution testing apparatus Type II (ERWEKA, DT600, Germany). The dissolution medium was 900 ml of phosphate buffer of pH 5.8 at a temperature of 37 ± 0.5 °C and 50 rpm. In all experiments, 5 ml of sample was withdrawn at 5, 10, 15, 20, 30 and 45 min and replaced with equal volume of fresh medium at the same temperature to maintain sink condition. Samples were filtered using Whatman No.1 filter paper and absorbances

were measured using UV/visible spectrophotometer (Spectronic® Genesys 5, Milton Roy Company, USA) at 243 nm after appropriate dilution with the phosphate buffer of pH 5.8. Percentage cumulative drug release was calculated using the equation obtained from a standard curve (USP 30/NF 25, 2007).

#### 2.3.6.8 Statistics

Statistical analysis to compare the effects of binders on granules and on the mechanical and release properties of the tablets was done using one-way analysis of variance (ANOVA) on a computer software SigmaStat® 3.5 for Windows (Systat Software, Inc. Point Richmond, USA). Tukey multiple comparision test was used to compare the differences between some properties of the different batches of granules and tablets. Moreover, computer software Origin7.0® (OriginLab Corporation, Northampton, USA) was used to draw figures showing results. At 95% confidence interval, *P* values less than or equal to 0.05 were considered significant. All the values are given as mean and standard deviation.

# 3. RESULTS AND DISCUSSIONS

## 3.1. Physicochemical characterization of the gum

### 3.1.1. Some common physicochemical properties of the gum

The gum was purified using water and alcohol 95% (v/v) as solvents. Table 3.1 shows some of the common physicochemical properties of the gum. The percentage yield of the gum obtained after purification was 49.6% (w/w), which is within the reported range of 40 - 60% (El-Ashry *et al*., 2003). The gum obtained was yellowish white in color. The swelling property of the gum was studied in distilled water and the result was found to be poor. The gum has high water solubility index. Upon chemical tests, the gum was found to be devoid of tannins and starch or dextrin using ferric chloride and iodine test solutions, respectively.

The moisture content of gum was 12.67% which is within the pharmacopoeial specification (maximum of 15%) set for acacia (BP, 2009). It is important to investigate the moisture content of a material because the economic importance of an excipient for industrial application lies not only on the cheap and ready availability of the biomaterial but also on the optimization of production processes such as drying, packaging and storage (Singh *et al*., 2010).

The total ash value of the gum was found to be 3.40% w/w which was within the pharmacopoieal specification ( maximum of 4%). Ash values reflect the level of adulteration or handling of the drug. Adulteration by sand or earth is immediately detected as the total ash is normally composed of inorganic mixtures of carbonates, phosphates, silicates and silica (Singh *et al*, 2010). Therefore, the low value of total ash obtained in this study indicates low levels of contamination during gathering and handling of the crude oleo-gum resin.

Knowledge of the pH of an excipient is an important parameter in determining its suitability in formulations since the stability and physiological activity of most preparations depends on pH (Singh *et al.*, 2010). The pH of the gum solution (5% w/v) at a temperature of 25 ºC was 5.43.This indicates that the gum is acidic in nature. This is

expected as gums are generally macromolecular acids (Odeku and Fell, 2004). This pH value is similar to the pH of *Acacia Senegal* (Azeez, 2005).

Table 3.1 Some common physicochemical properties of myrrh gum (n = 3, mean ± SD).

| Parameter | Value |
|---|---|
| Color | Yellowish white |
| Yield value (%) | 49.60 ± 1.01 |
| Swelling power (ratio) | 1.98 ± 0.60 |
| Water solubility index (%) | 56.67 ± 3.06 |
| Loss on drying (%) | 12.67 ± 1.53 |
| Total ash (%) | 3.40 ± 0.37 |
| Tannin content | Absent |
| Starch or dextrin content | Absent |
| pH of mucilage | 5.43 ± 0.06 |

### 3.1.2 Relative solubility of the gum

Solubility values presented in Table 3.2 show that the gum is freely soluble in hot water and soluble in cold water. The solubility of the gum in water may be due to the branched nature of the polymer which has been reported to be more soluble compared with linear molecules (Lima *et al*., 2002). It was also indicated that the gum is insoluble in the organic solvents (acetone, chloroform and ethanol). The insolubility of the gum is due to hydrophilicity of macromolecules (Mahmud *et al*., 2008).

Table 3.2 Solubility of the myrrh gum in different solvents (n = 3, mean ± SD).

| Solvent | Solubility (g/ml) | Solubility (%) |
|---|---|---|
| Cold distilled water | 0.094 ± 0.008 | 9.40 ± 0.83 |
| Hot distilled water | 0.103 ± 0.008 | 10.33 ± 0.81 |
| Alcohol | 0.010 ± 0.004 | 1.00 ± 0.40 |
| Acetone | 0.005 ± 0.001 | 0.53 ± 0.12 |
| Chloroform | 0.003 ± 0.001 | 0.27 ± 0.12 |

### 3.1.3 Moisture sorption-desorption property

The water sorption-desorption result presented in Fig. 3.1 shows that the gum absorbs substantial amount of water when stored in high humidity environment. The amount of water sorption increased steadily to a saturation point in 5 days. In the presence of desiccant, the water was rapidly lost within a few days. Similar trend was observed with cashew gum (Abdulsamad, 2004). The implication of this is that the gum, when stored in damp environment can easily be susceptible to microbial and physicochemical deterioration as a result of high moisture content. Furthermore, the integrity of the gum can be maintained when stored in air-tight containers and in the presence of desiccants (Mahmud *et al*, 2008).

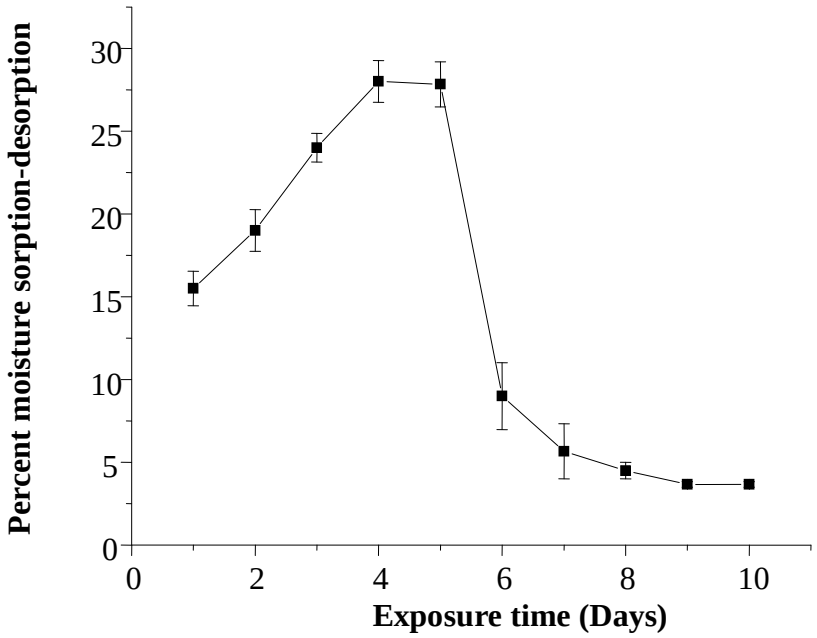


Figure 3.1. Percentage moisture sorption-desorption pattern of myrrh gum powder (n=3).

### 3.1.4 Flow properties of the gum powder

Density and density related properties of the gum are presented in Table 3.3. The Carr's index, Hausner ratio and angle of repose of the gum were 5.82%, 1.06 and 25.79°, respectively, implying that the gum has excellent flow properties with excellent compressibility. This is important in scale up processes involving this material as an excipient in a pharmaceutical formulation. Modification of formulations containing this gum for the improvement of flow properties during process development will therefore be minimal (Singh *et al.*, 2010).

The bulk and tapped densities give an insight on the packing arrangement of the particles and the compaction profile of a material. The Carr's index and Hausner ratio are the measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free flowing powder, such interactions are generally less significant, and bulk and tapped densities will be closer in value. For poorly flowing materials, there are frequently greater interparticulate

interactions, and a greater difference between bulk and tapped densities are observed. These differences are reflected in Carr's index and Hausner ratio (USP 30/NF 25, 2007).

Table 3.3 Flow properties of the myrrh gum powder (n = 3, mean ± SD).

| Variables | Values |
|---|---|
| Bulk density (g/ml) | 0.75 ± 0.006 |
| Tapped density (g/ml) | 0.80 ± 0.010 |
| Carr's index (%) | 5.82 ± 1.370 |
| Hausner ratio | 1.06 ± 0.020 |
| Flow rate (g/sec) | 18.32 ± 4.050 |
| Angle of repose (Ɵ) | 25.79 ± 0.710 |

### 3.1.5 Viscosity of gum mucilages

Fig. 3.2 shows the comparative effect of concentration on the viscosity of the myrrh gum, PVP K-30 and acacia gum. Viscosity of mucilages increased with increase in gum concentration. The figure also shows that the viscosity of the myrrh gum at a concentration of 5% w/v and above increases much higher than the viscosities of PVP K-30 and acacia. Comparison of the mean viscosity values indicated that the myrrh gum at 7.5 and 10% w/v concentrations has significantly higher viscosities than the viscosities of the respective concentrations of PVP K-30 and acacia gum ($p < 0.05$). Gums with high viscosities are said to have better quality than less viscous gums for use as a binder and matrix forming agent (Ofori-kwakye *et al*., 2010).

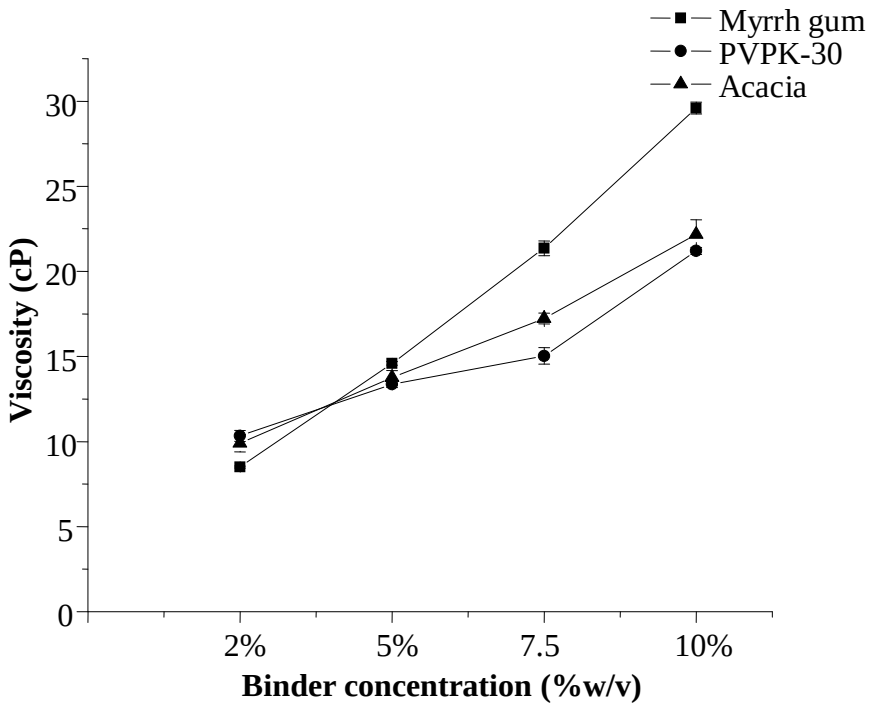


Figure 3.2 The effect of concentration on the viscosity of the myrrh gum, PVP K-30 and acacia at 25 °C.

### 3.1.6 Fourier transform-infrared study

Chemical-chemical interactions are studied in various ways using various sophisticated instruments like FTIR, DSC etc. In the present study, interactions between the myrrh gum and paracetamol have been studied using FTIR spectra (Fig. 3.3-3.5). Fig. 3.3 depicts the FTIR spectrum of the gum, Fig. 3.4 shows the FTIR spectrum of paracetamol without the gum and Fig. 3.5 demonstrates the FTIR spectrum of paracetamol along with the gum. When the figures were compared, it was found that there were no physical and chemical interaction between the gum and paracetamol as there were no distinct changes in the available peaks with the corresponding wave numbers in Fig. 3.4 and 3.5. The principal peaks in the FTIR spectrum of paracetamol are 1650 $cm^{-1}$, 1563 $cm^{-1}$ and 1443 $cm^{-1}$ (Clarke, 1975). These major peaks of paracetamol in FTIR spectrum of the mixture were not changed confirming that there were no interactions between paracetamol and myrrh gum. Wave numbers between 4000 and 2800 $cm^{-1}$ are the stretching zone of C-H(alkenes) (3000-2850 $cm^{-1}$ ), C-H (Aromatic) (3100-3000 $cm^{-1}$ ), OH (Alcohol) (3700-

3200 $cm^{-1}$ ), C-H (alkenes) (3100-3000 $cm^{-1}$ ), wave numbers between 1690 and 1620 are the stretching zone of C = N (1690-1620 $cm^{-1}$ ).

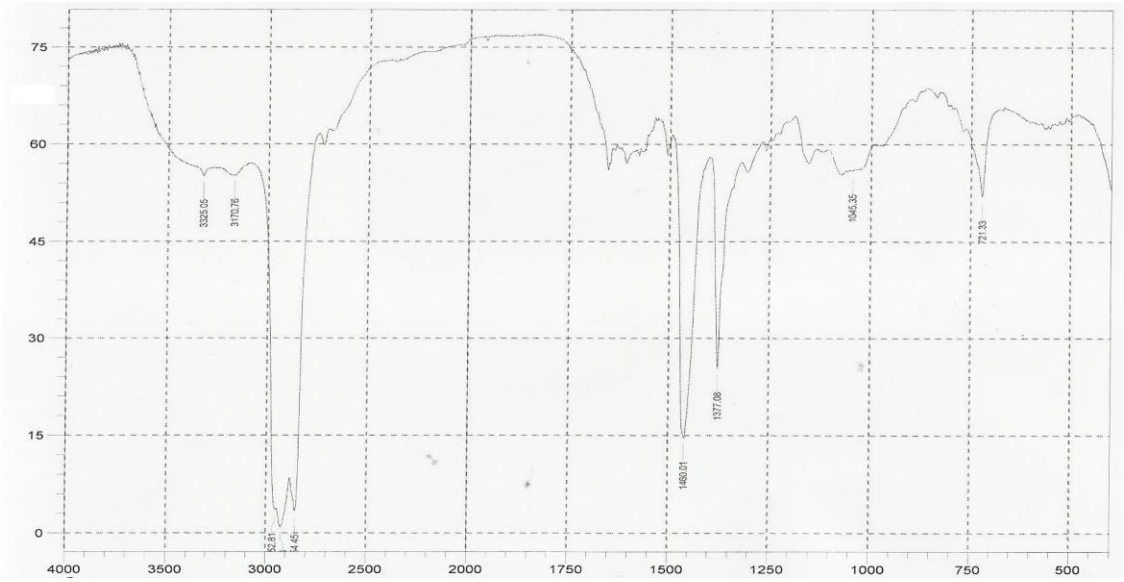


Figure 3. 3 FTIR spectrum of the Wave number.

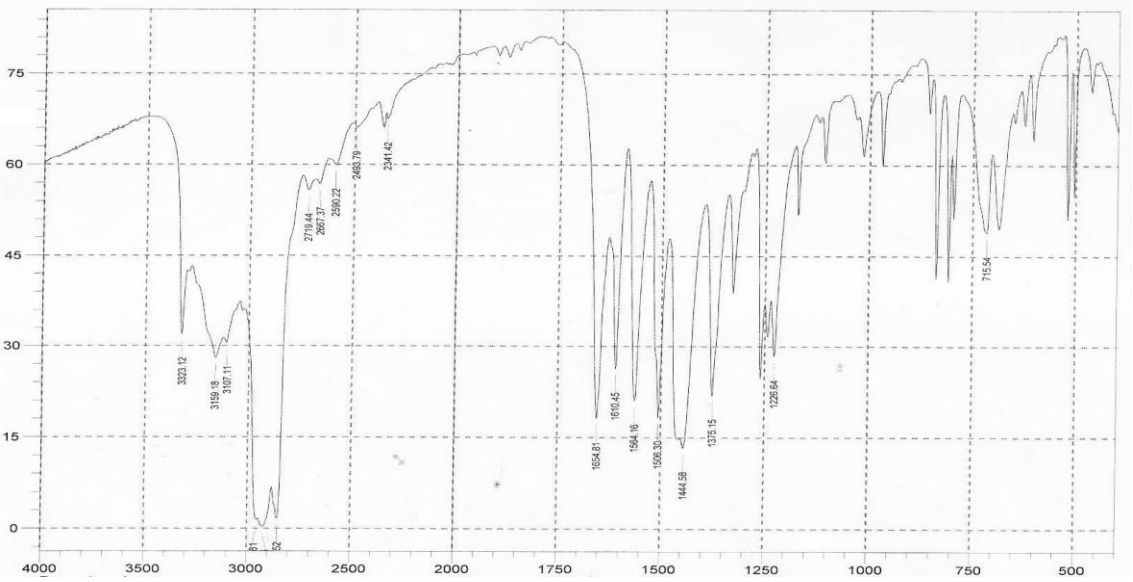


Figure 3. 4 FTIR spectrum of paracetamol.

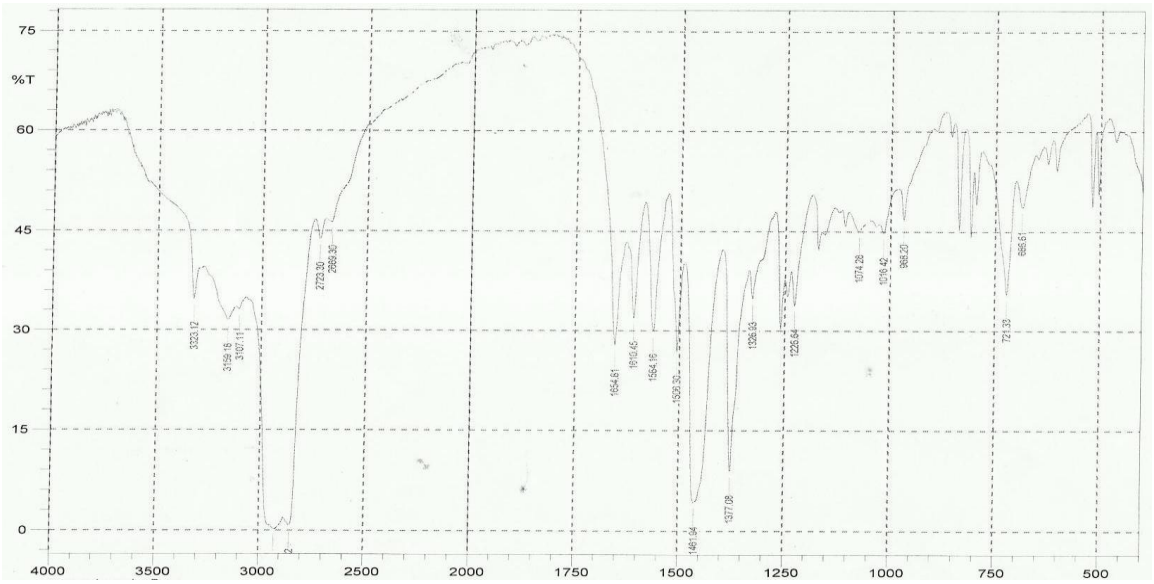


Figure 3.5 FTIR spectrum of paracetamol along with the myrrh gum.

## 3.2 Evaluation of granules

### 3.2.1 Particle size and size distribution of granules

Particle size distribution of granules is evaluated due to the impact of granule size on flowability, uniformity of weight and content, compression, dissolution and subsequently drug release (Fichtner *et al*., 2005; Virtanen *et al*., 2010). Particle size and particle size distribution affect the compatibility and rearrangement of particles (Virtanen *et al*., 2010). Though, there are exceptions, the flow properties of granules are improved when the particles are large and the particle size distribution is narrow. However, larger particles lead to less strong tablets due to the fact that they have lesser surface areas for bond formation as compared to smaller particles (Sun and Himmelspach, 2006). Hence, an optimal particle size and size distribution is required to obtain good flow properties, compaction and hardness. The particle size of paracetamol granules were increased as the concentration of the binders increased as shown in Fig. 3.6 and the size distribution is presented in Fig. 3.7. There were optimum amount of fine particles which implied that the granules may have good flow properties. Moreover, presence of an optimum percent of fine particles may indicate that there would be less unfilled voids during the process of compression which may lead to less hard and less friable tablets.

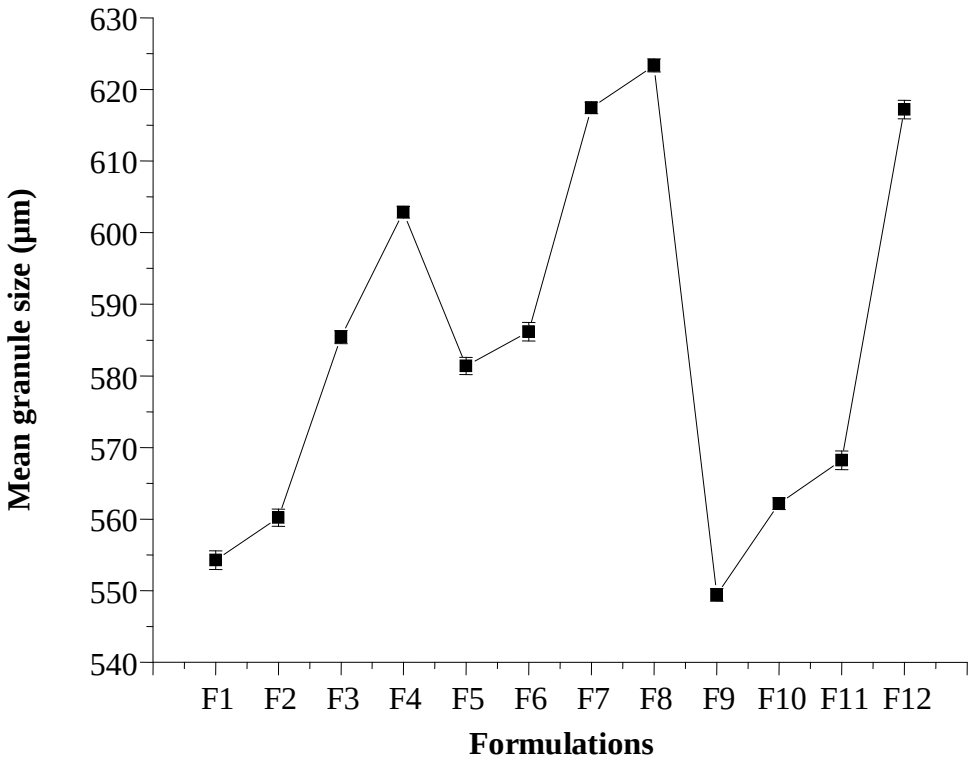


Figure 3.6 Particle sizes of paracetamol granules prepared with different concentrations of myrrh gum, PVP K-30 and acacia as binders.

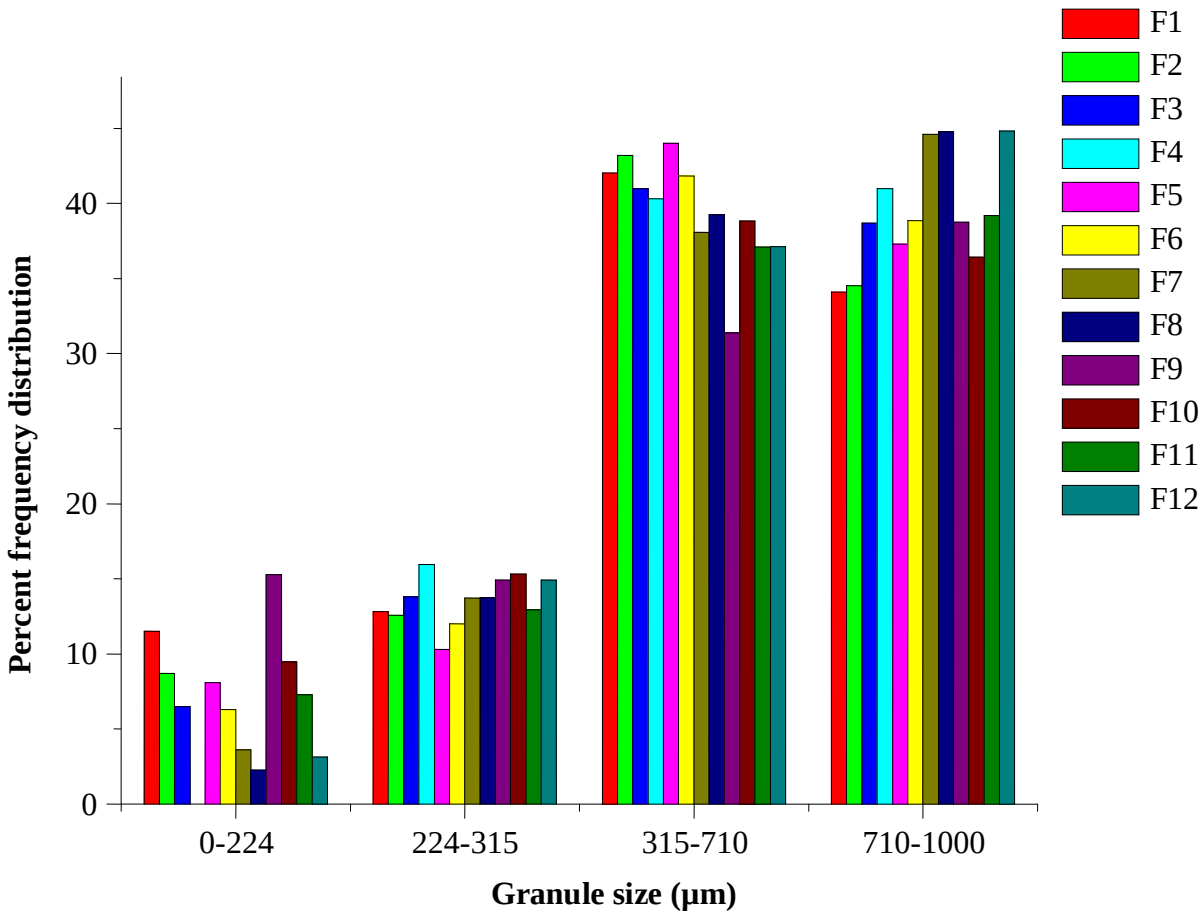


Figure 3.7 Particle size distributions of granules of paracetamol prepared with different concentrations of myrrh gum, PVP K-30 and acacia

### 3.2.2 Density and density related properties

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 Table 3.4, the bulk and tapped densities of the granules decrease with increasing concentrations of the binders. This could be attributed to the increase in the proportion of larger granules greater than 315 μm with increasing binder concentrations. The granules occupy larger volumes making the bulk density value lower than smaller granules which occupy smaller bulk volumes (Singh *et al*., 2010).

Comparison of granules indicate that granules prepared with 5%, 7.5% and 10% w/w concentrations of the myrrh gum have exhibited significantly higher bulk and tapped densities than those granules containing respectively similar concentration of PVP K-30 and acacia ($p < 0.05$). Table 3.4 also show that all granules have Carr's compressibility index less than 10% and Hausner ratio of less than 1.10. Therefore, all the granules prepared exhibited excellent flow properties and compressibility.

Table 3.4 Bulk and tapped densities, and density related properties of paracetamol granules (n = 3, mean ± SD).

| Formulation | Bulk density (g/ml) | Tapped density (g/ml) | Carr's index (%) | Hausner ratio |
|---|---|---|---|---|
| F1 | 0.61 ± 0.010 | 0.64 ± 0.006 | 4.69 ± 0.017 | 1.05 ± 0.000 |
| F2 | 0.60 ± 0.000 | 0.62 ± 0.000 | 4.25 ± 0.000 | 1.09 ± 0.000 |
| F3 | 0.55 ± 0.000 | 0.57 ± 0.000 | 3.49 ± 0.000 | 1.04 ± 0.000 |
| F4 | 0.53 ± 0.010 | 0.55 ± 0.006 | 4.82 ± 0.017 | 1.07 ± 0.000 |
| F5 | 0.59 ± 0.010 | 0.62 ± 0.006 | 5.38 ± 1.048 | 1.06 ± 0.012 |
| F6 | 0.52 ± 0.010 | 0.54 ± 0.006 | 4.28 ± 0.017 | 1.05 ± 0.000 |
| F7 | 0.50 ± 0.000 | 0.52 ± 0.000 | 3.21 ± 0.000 | 1.03 ± 0.000 |
| F8 | 0.47 ± 0.010 | 0.50 ± 0.006 | 5.32 ± 2.110 | 1.05 ± 0.020 |
| F9 | 0.62 ± 0.010 | 0.64 ± 0.001 | 4.15 ± 0.035 | 1.04 ± 0.000 |
| F10 | 0.54 ± 0.010 | 0.56 ± 0.010 | 3.54 ± 0.783 | 1.04 ± 0.012 |
| F11 | 0.52 ± 0.015 | 0.55 ± 0.015 | 4.23 ± 1.380 | 1.05 ± 0.020 |
| F12 | 0.49 ± 0.010 | 0.51 ± 0.010 | 3.97 ± 0.005 | 1.04 ± 0.012 |

### 3.2.3 Granule flow rate and angle of repose

As indicated in Table 3.5, angle of repose decreased as the binder concentration increases and the values for all the granulations were below 30° suggesting excellent granule flow properties. Angle of repose is a measure of powder resistance to flow under gravity due to frictional forces resulting from the surface properties of the granules. It decreases as binder content of the granules increases. This may be attributed to the reduced cohesive forces of the larger granules formed at higher binder concentration (Onunkwo, 2010). Granules formulated with the myrrh gum had the highest flow rate at 7.5% w/w binder concentration. The large average granule size formed at high binder concentration of the binder may have affected the flow rate. Large granule size has been shown to obstruct the

flow through funnel orifice especially when the granule size approaches the size of the orifice diameter (Onunkwo, 2010).

Table 3.5 Angle of repose and flow rate of paracetamol granules (n = 3, mean ± SD).

| Formulation | Angle of repose (Θ) | Flow rate (g/sec) |
|---|---|---|
| F1 | 27.68 ± 2.130 | 16.89 ± 0.431 |
| F2 | 27.08 ± 0.683 | 17.68 ± 2.169 |
| F3 | 25.83 ± 1.270 | 17.96 ± 1.380 |
| F4 | 25.46 ± 0.934 | 15.13 ± 1.326 |
| F5 | 27.41 ± 0.924 | 16.94 ± 0.350 |
| F6 | 26.71 ± 1.311 | 17.48 ± 1.807 |
| F7 | 25.65 ± 0.790 | 17.76 ± 0.418 |
| F8 | 25.40 ± 0.914 | 15.49 ± 0.856 |
| F9 | 27.01 ± 1.526 | 15.44 ± 1.123 |
| F10 | 26.48 ± 0.973 | 16.22 ± 1.199 |
| F11 | 25.42 ± 0.690 | 16.23 ± 2.206 |
| F12 | 25.05± 1.468 | 14.45 ± 1.111 |

### 3.2.4 Granule friability

Granule friability is one indicator of the ability of a given binder to form a compacted mass during the granulation process. It is the measure of granules' resistance to dust upon an impact stress. The results of the friability tests of the different batches of granules are shown in Fig. 3.8. The results indicate that friability values of the granules decrease with increasing binder concentration. Generally, friability values of the granules prepared with the myrrh gum were less than those of acacia and comparable to PVP K-30. As their comparison indicates, there was no significant difference in the percent friability values between myrrh gum and the reference binders at all binder concentrations except at 2% concentrations ($p > 0.05$). At 2% concentrations, granules prepared with myrrh gum showed significantly higher friability than those prepared with PVP K-30 ($p < 0.05$).

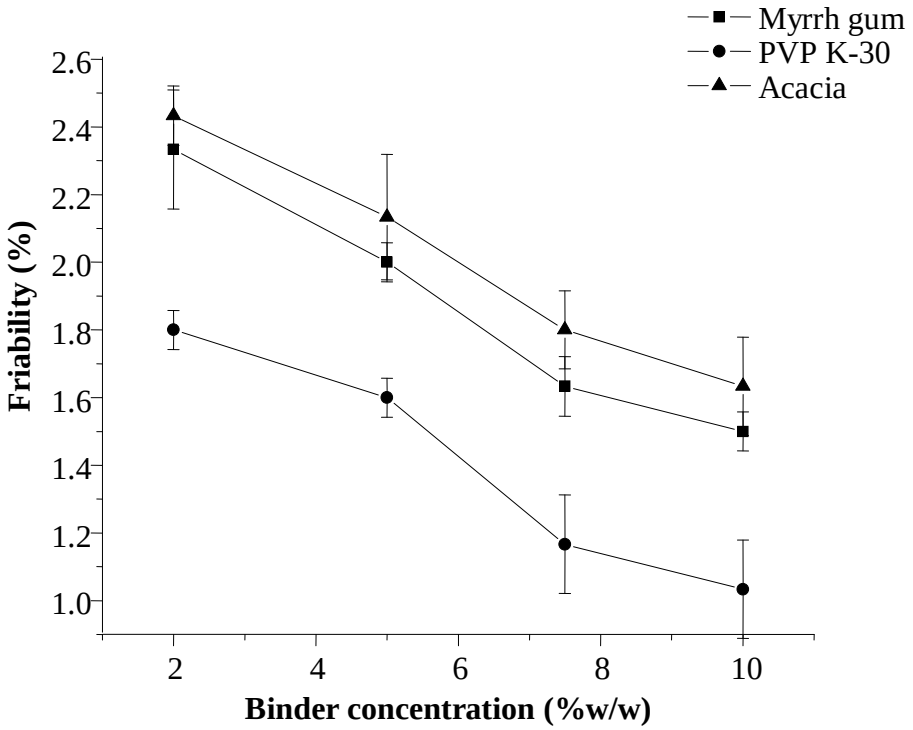


Figure 3.8 Friability of granules prepared with different concentrations of myrrh gum, acacia and PVP K-30.

## 3.3 Evaluation of tablets

### 3.3.1 Weight uniformity and thickness

Uniformity of weight and thickness are indications of the amount of API in a batch of tablets. However, these do not assure that the API is uniform in all tablets especially in formulations with low dose concentrations. Furthermore, if weight, thickness or diameter of tablets in a batch varies, there will be variations in disintegration and dissolution. The compendial specification for uniformity of weight states that for tablets weighing more than 324 mg, weights of not more than two tablets should deviate from the average weight by more than 5% (USP, 2007). All the tablets have a diameter of 10 mm which is already fixed by the diameter of the die cavity of the tablet machine. Weight uniformity and thickness of tablets are given in Table 3.6. The weight of tablets prepared using different binders and at various concentrations met the compendial specification with no significant difference in these values ($p > 0.05$).

Table 3.6 Weight and thicknesses of the different formulations of paracetamol tablets (n=20, mean ± SD).

| Formulation | Weight (g) (mean ± SD) | Thickness (mm) (mean ± SD) |
|---|---|---|
| F1 | 0.418 ± 0.050 | 3.07 ± 0.06 |
| F2 | 0.422 ± 0.015 | 3.10 ± 0.06 |
| F3 | 0.407 ± 0.049 | 3.10 ± 0.00 |
| F4 | 0.420 ± 0.012 | 3.07 ± 0.06 |
| F5 | 0.415 ± 0.014 | 3.10 ± 0.00 |
| F6 | 0.417 ± 0.016 | 3.10 ± 0.00 |
| F7 | 0.421 ± 0.012 | 3.07 ± 0.06 |
| F8 | 0.409 ± 0.051 | 3.10 ± 0.00 |
| F9 | 0.422 ± 0.011 | 3.03 ± 0.06 |
| F10 | 0.421 ± 0.014 | 3.10 ± 0.10 |
| F11 | 0.423 ± 0.011 | 3.10 ± 0.00 |
| F12 | 0.420 ± 0.014 | 3.10 ± 0.00 |

### 3.3.2 Crushing strength, tensile strength and friability

Crushing strength shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. It is the property of a tablet that is measured to assess its resistance to permanent deformation. Furthermore, the mechanical strength of a tablet determines the disintegration time and the rate of dissolution. As the concentration of the binder increases, the mechanical strength increases (Allen *et al*., 2004).

As shown in Fig. 3.9, the crushing strength of tablets increased with increased concentration of binders used. Moreover, tablets prepared with myrrh gum showed significantly higher crushing strengths than the respective concentrations of acacia ($p \leq 0.05$). However, there was no significant difference in the crushing strengths of tablets prepared with myrrh gum and PVP K-30 ($p > 0.05$) except at 2% concentration the

crushing strength of tablets prepared with myrrh gum was significantly higher than those of PVP K-30 ($p \leq 0.05$).

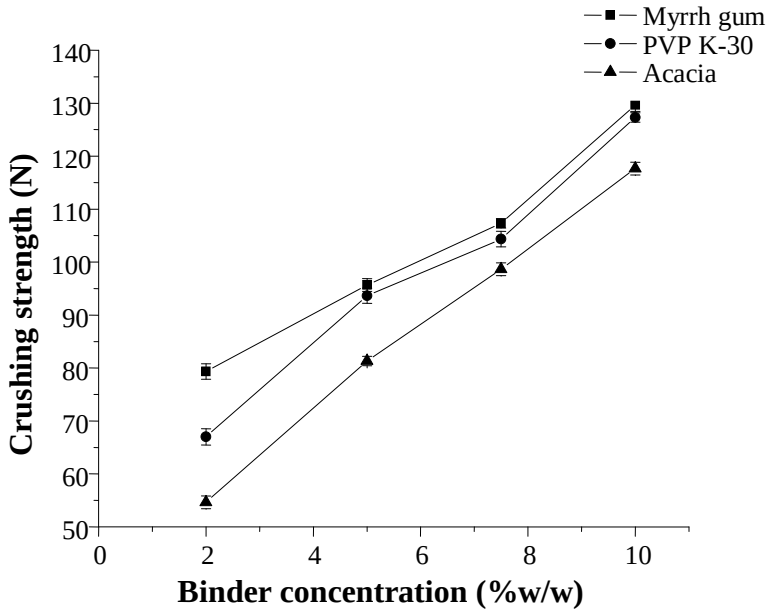


Figure 3.9 Effect of binder concentration on the crushing strengthes of paracetamol tablets.

The tensile strength of paracetamol tablets containing different concentrations of the myrrh gum and reference binders are presented in Fig. 3.10. Generally, the values increase with an increase in binder concentration. It has been established that the presence of high concentration of plasto-elastic binding agent leads to an increase in plastic deformation of the formulation and consequently to the formation of more solid bonds with an increase in tablet strength and resistance to fracture (Adetogun and Alebiowu, 2009). The results indicate that tablets prepared with myrrh gum have significantly higher tensile strengths than tablets prepared with acacia as a binder with similar concentrations ($p < 0.05$). However, there was no significant difference in tensile strengths between tablets prepared with myrrh gum and PVP K-30 ($P > 0.05$) except at 2% concentration where there is significantly higher tensile strength of tablets prepared with myrrh gum than with PVP K-30 ($p < 0.05$).

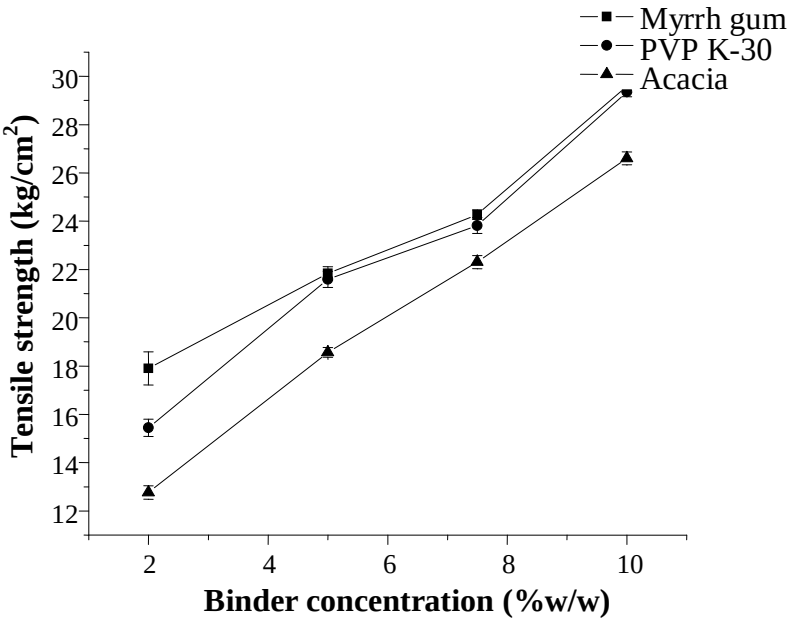


Figure 3.10 Effect of binder concentration on the tensile strengthes of paracetamol tablets.

Friability is another measure of the mechanical property of tablets with compendial specification of less than 1% (USP, 2007). Friability decreases with increase in percentage of binders. Friability is especially important because the tablet is subjected to various abrasive motions during production and use (Adebayo & Itiola, 2003). As shown in Fig. 3.11, the friability of the tablets decreased as the concentration of the binder increased. However, paracetamol tablets prepared with 2% of myrrh gum, PVP K-30 and acacia failed to meet friability tests (>1%). Tablets prepared with myrrh gum as a binder at concentrations more than 2% met the compendial specification for friability with the values significantly smaller than acacia ($p < 0.05$) and comparable to PVP K-30 ($p > 0.05$). This suggests that at 5% concentration and above, the myrrh gum should be able to keep the tablets intact and withstand abrasive motions during handling.

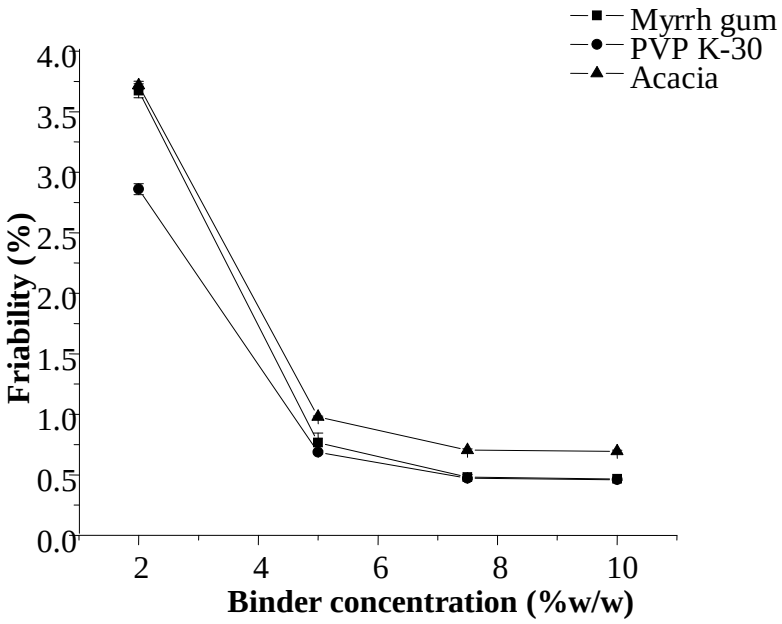


Figure 3.11 Effect of binder concentration on the friability of paracetamol tablets.

### 3.3.3 Disintegration tests

Disintegration is a crucial step in the release of drugs from immediate release dosage forms. The rate of disintegration is directly proportional to the rate of dissolution. The rate of disintegration is influenced by the rate of influx of water into the tablets which is also dependent on the porosity of the tablets. When the porosity is high, disintegration is hardly influenced by tablet formulation; otherwise, disintegration will be affected by the excipients (Bi *et al*., 1999). Disintegration time increases with increase in concentration of binder. Delay in disintegration time could be attributed to the gum facilitated extensive plastic deformation, leading to an increase in the area of contact between particles, reducing rate of fluid penetration into interstitial void spaces. This results in reduction of swelling of the disintegrants and disruption of the tablet, and consequently with prolonged disintegration time (Odeku & Itiola, 2003).

The disintegration time generally increases with increased relative density of the tablets and with an increase in binder concentration. The disintegration profile of tablets prepared with different concentrations of binders is depicted in Fig. 3.12. The observed increase in the disintegration time of the tablets as the concentration of the gum binder

increased from 2% w/w to 10% w/w is due to an increase in bond formation. Tablets containing myrrh gum generally showed significantly longer *(*$p < 0.05$*)* disintegration time than tablets containing PVP K-30 except at 10% concentration and no significant difference with tablets containing acacia ($p > 0.05$). Furthermore, all the tablets conformed to the British Pharmacopoeia (BP, 2009) requirements for uncoated tablets on disintegration, *i.e.*, disintegration within 15 min, except for formulations containing 10% myrrh gum and acacia with a disintegration time of 18.73 and 19.72 min, respectively.

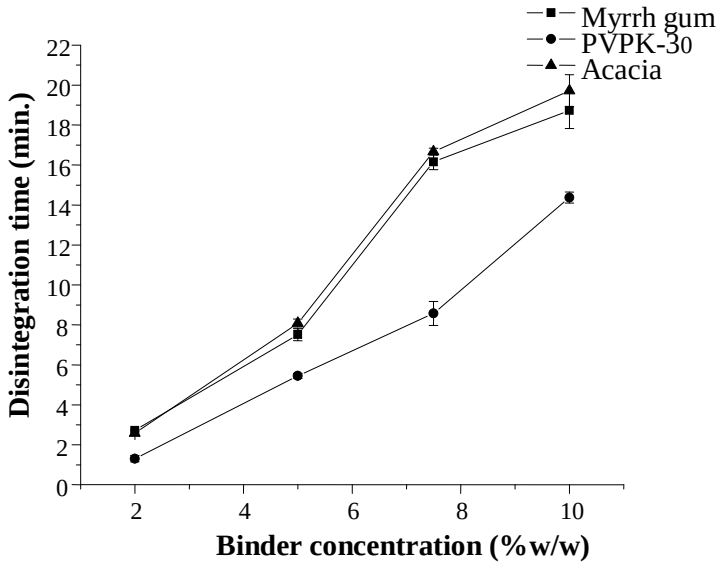


Figure 3.12 Effect of binder concentration on the disintegration time of paracetamol tablets.

### 3.3.4 Calibration curve

The UV absorption calibration curve of paracetamol reference standard (Fig. 3.13) in phosphate buffer of pH 5.8 at 243 nm at six different concentrations yielded a linear curve with a regression equation of $A = 65.34C + 0.031$ (where, A is the absorbance and C is the concentration in mg/ml).

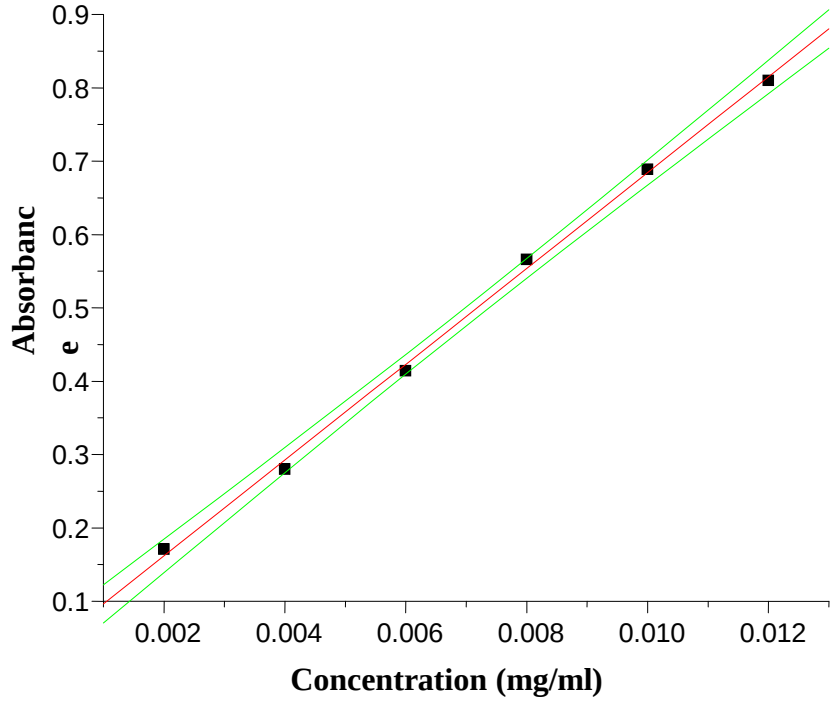


Figure 3.13 Calibration curve of paracetamol reference standard in pH 5.8 phosphate buffer at 243 nm with 95% confidence interval ($r^2$ = 0.998).

### 3.3.5 *In vitro* drug release studies

*In vitro* drug release profiles of the tablets prepared with different concentrations of the binders (at pH 5.8) are presented in figures 3.14 (a), 3.14 (b), 3.14 (c) and 3.14 (d). As the binder concentration increased, there was a general decrease in the release rate of paracetamol from the tablets. This might be attributed to the sticky film of hydration on the surface that occurs at high binder concentration reducing the diffusion of the drug. The figures also reveal that tablets made with PVP K-30 provide the highest drug release while those prepared with acacia show the lowest. As the concentration of binders increased from 2 to 10%, the drug release rate decreased. The myrrh gum showed less drug release rate than PVP K-30 because of more binding property; the gums in higher concentration produced tablets with dense matrix around the drug particles, providing more barrier for tablets to escape and dissolve (Girhepunje *et al*., 2009).

The tablets made with the myrrh gum as a binder gave significantly higher dissolution profile than did acacia with respective concentrations at 2 %, 5% and 10% w/w *(*$p \leq 0.05$*)* and comparable profile at 7.5% w/w concentration ($p > 0.05$). Moreover, the myrrh gum tablets have no significant drug release profile than PVP K-30 tablets at 5%, 7.5% and 10% w/w concentrations ($p > 0.05$) and have significantly lower drug release profile than PVP K-30 at 2% w/w concentration *(*$p < 0.05$*)*.

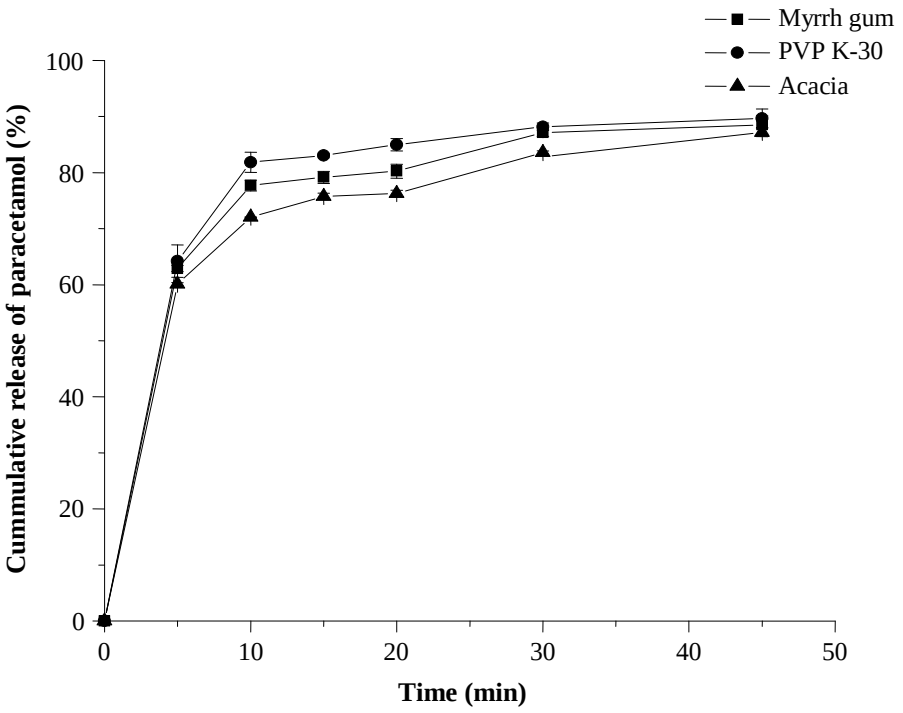


Figure 3.14 (a) *In vitro* release profile of paracetamol from tablets prepared with 2% binder concentration (n = 6, mean ± SD).

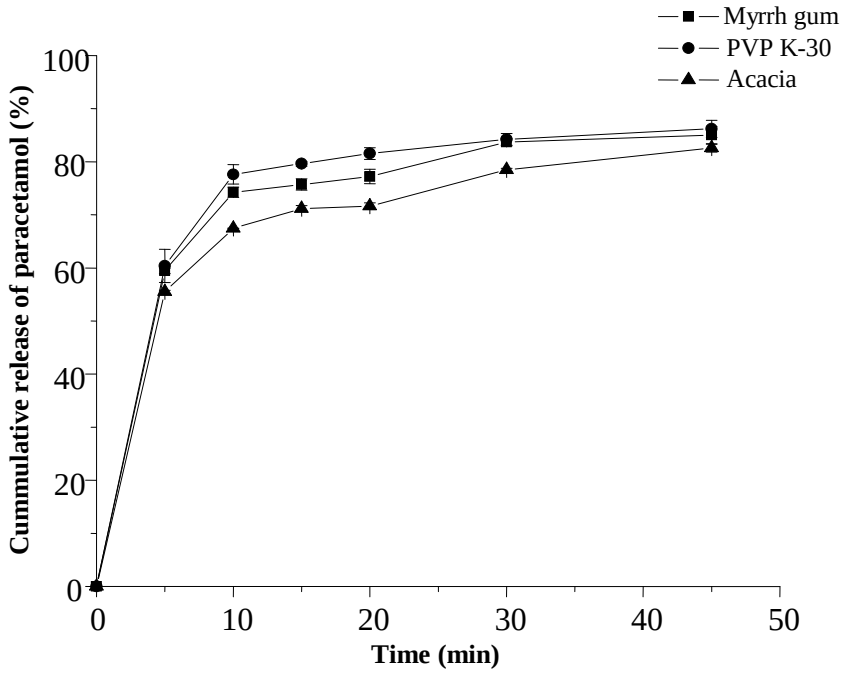


Figure 3.14 (b) *In vitro* release profile of paracetamol from tablets prepared with 5% binder concentration (n = 6, mean ± SD).

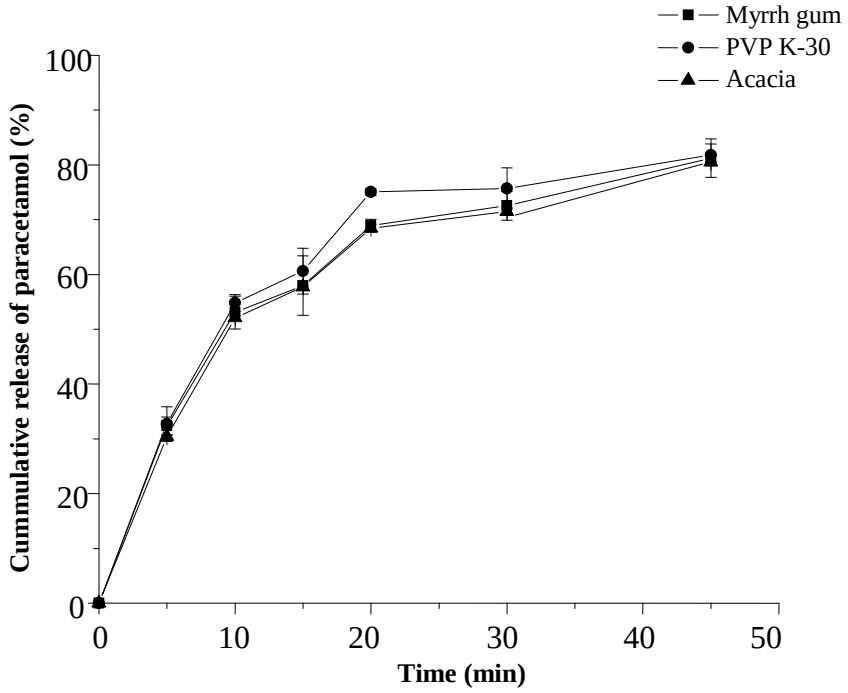


Figure 3.14 (c) *In vitro* release profile of paracetamol from tablets prepared with 7.5% binder concentration (n = 6, mean ± SD).

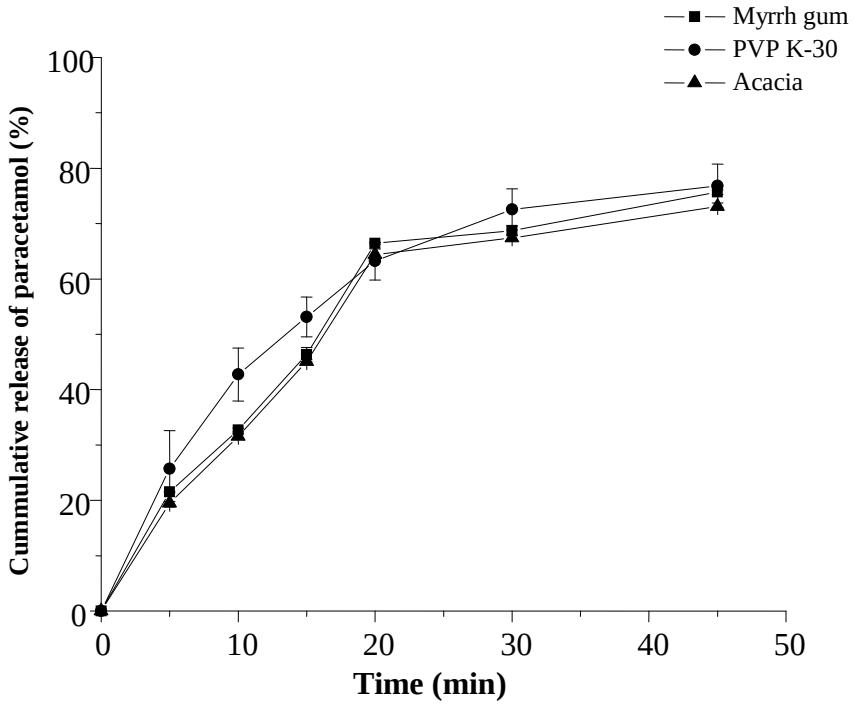


Figure 3.14 (d) *In vitro* release profile of paracetamol from tablets prepared with 10% binder concentration (n = 6, mean ± SD).

# 4. CONCLUSION

This study provided an insight into the evaluation of a gum extracted from local myrrh as a binder in granule and tablet formulations using paracetamol as a model drug. Extraction of the gum provided considerable yield of purified gum. The physicochemical characteristics of the gum indicated that the gum is soluble in cold water and freely soluble in hot water, poor swelling power, good viscosity, acceptable moisture content, high moisture sorption and no tannin and starch/dextrin and small ash value, with excellent flowability and compressibility.

The granules prepared by wet granulation of paracetamol and the gum exhibited increase in granule size with concentration and uniform size distribution, acceptable flow properties as indicated by their Carr's indices, Hausner ratios and angles of repose, and decreased friability with increasing binder concentrations which were comparable to those prepared with reference binders.

All of the prepared tablets exhibited more or less comparable physical and mechanical properties with respect to crushing strength, tensile strength, friability, uniformity of weight, and disintegration time. Tablets prepared with the myrrh gum showed higher crushing strengths and tensile strengths than those prepared with the reference binders. Regarding the disintegration time, tablets prepared with the gum had longer disintegration time than those prepared with PVP K-30 except at 10% w/w concentrations and comparable to those prepared with acacia. The drug release studies of the tablets indicated that tablets prepared with myrrh gum binder exhibited higher release profile than acacia and a little lesser release profile than PVP K-30 tablets.

From the foregoing it can be concluded that gum extract of local myrrh (*Commiphora myrrha* syn. *C. molmol)* could be positively explored as an alternative excipient for its binding ability in granule and tablet formulations.

# 5. SUGGESTIONS FOR FURTHER STUDIES

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

- Detailed physicochemical characterization of the gum such as particle size distribution and morphological characterization;
- Stability studies of tablets prepared with the myrrh gum;
- Optimization of myrrh gum concentration for conventional tablet use;
- *In vitro -in vivo* correlation of the dissolution pattern and drug release.

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