Formulation and Evaluation of Acetaminophen Suspension using Fenugreek Seeds as a Natural Suspending Agent

A project submitted

by

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I dedicate my work to my wife, parents and supervisor

Certification Statement

This is to certify that this project titled 'Formulation and Evaluation of Acetaminophen Suspension using Fenugreek Seeds as a Natural Suspending Agent' submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Zara Sheikh, Senior Lecturer and Academic Coordinator, Department of Pharmacy, BRAC University and that appropriate credit is given where I have used the language, ideas or writings of another.

Signed,

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Countersigned by the supervisor

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ABSTRACT

A great number of pharmaceutical excipients, both natural and synthetic, are available to meet the demands of the rapid development of the pharmaceutical industry. Nowadays, naturally derived excipients are preferred over synthetic excipients owing to their greater availability in nature, biocompatibility, biodegradability, non-toxicity, environment friendliness and cost-effectiveness. A good example of a natural source of excipient is *Trigonella foenum graceum* (Family: Leguminosae) seeds, also known as fenugreek seeds, which contains a high percentage of mucilage and forms viscous tacky mass that swells up when exposed to fluids and thus can be used as a suspending agent in pharmaceutical suspensions. The aim of the present study was to utilize fenugreek mucilage as a natural suspending agent by formulating and evaluating a suspension containing acetaminophen as the active pharmaceutical ingredient and incorporating fenugreek mucilage as the suspending agent. Five formulations (FS1 – FS5) each containing varying proportions of *Trigonella foenum graceum* mucilage, were prepared. The suspensions were subjected to evaluation by studying different parameters like pH, sedimentation volume, degree of flocculation, viscosity, redispersibility, flow rate, effect of temperature on viscosity and finally the rate of release of drug within twenty minutes. pH of all the formulations were found to be similar (approximately 7.8). The sedimentation volume did not change significantly over a period of 45 days indicating higher degree of flocculation and good stability of the suspensions. The suspensions were easily redispersible after shaking only twice even after 45 days and the flow rate of the suspensions did not differ much suggesting that suspensions with 2 gm of mucilage (FS4) can be used instead of FS3 (with 1.5 gm of mucilage) as it gives a higher degree of flocculation. The dissolution results of the suspensions were found to be satisfactory since on an average 65-70% of the drug was released within 20 minutes, thus complying with USP specifications. Even though all the formulations gave good results, it can be concluded that FS4 formulation is the optimum formulation with greater flocculation, good flow rate and easily redispersibility characteristics along with a good percentage release of drug within twenty minutes. These formulations can be compared with the market preparations for further evaluation.

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INTRODUCTION

1. INTRODUCTION

1.1 Background

With the fast growing development of pharmaceutical industry it has become a challenge to discover newer compounds to meet up demands of the rapid development. A great number of pharmaceutical excipients, both natural and synthetic excipients, are available (Nayak A. K., Pal, Pradhan, & Ghorai, 2012). Recently the reason behind preferring naturally derived excipients over synthetic excipients is due to the vast availability of natural plant based excipients and the natural sources can assure non-stop supply at a minimal cost (Goswami & Naik, 2014). Plant mucilage like acacia are immensely used in pharmaceutical dosage forms as suspending agents and also as binders (Upadhyay, 2017). These plant based excipients have been used to prepare various types of dosage forms where they have proved their applicability and efficacy (Kilor & Bramhe, 2014). Suspending agents are a prerequisite in suspension formulation to manufacture stable formulations and reduce settling of the particles along with ease of redispersion (Doye, Mena, & Das, 2017). Various plant mucilages have been reported that their use is exceptionl and has demand like mucilages that is obtained from *Buteamono spermama, Albizia zygia* gum and *Leucaena eucocephala* seed gum (Nair & Fahsa, 2013).

1.2 Rationale of the Study

Naturally derived excipient has become widely accepted along with synthetic excipients. Naturally derived excipients are used as substitutes for the synthetic excipients due to their greater availability in nature, biocompatibility, biodegradability, non-toxicity, environment friendliness and cost-effectiveness. These naturally derived excipients can be used in varied dosage forms and has no hazardous effect on the active pharmaceutical ingredients (Bhosale, Osmani, & Moin, 2014). *Trigonella foenum graceum* (Family: Leguminosae) seeds, also known as fenugreek seeds, it has mucilage in great amount and forms viscous tacky mass

and swell up when exposed to fluids (Bhandare, Kavade, & Surse, 2005). Therefore the potential of fenugreek seeds as suspending agents can be exploited for use in suspensions.

1.3.1 Aim

The study is to assess the stability of acetaminophen suspension formulated with fenugreek seeds (a natural suspending agent) and compare the release rate differences with the marketed acetaminophen suspension.

1.3.2 Objectives

Objectives of the study are as follows:

1. Extract the suspending agent from *Trigonella foenum graecum* seeds (fenugreek seeds).

2. To formulate acetaminophen suspensions containing various proportions of mucilage of fenugreek seed as a suspending agent.

3. To evaluate the formulated suspensions by determining pH, sedimentation volume, redispersibility, degree of flocculation etc.

4. To determine the rheological properties of the formulated acetaminophen suspensions.

5. To compare the release rates of the formulations.

CHAPTER 2

LITERATURE REVIEW

2. LITERATURE REVIEW

2.1 Fenugreek

The scientific name of Fenugreek is *Trigonella foenum-graecum,* commonly known as methi and it belongs to Leguminosae family. It is used all around the world for various purposes. It is mostly used as a flavor component on various types of food (Pasricha & Gupta, 2014). It has good binding properties and used as suspending agent (Wani & Kumar, 2016). The main components of the seeds are carbohydrates, mucilage's, proteins, fixed oils, flavonoids and saponins. At low concentration level, fenugreek produces high viscosity of mucilage (Kumar, Singhal, Bansal, & Gupta, 2014). It is reported that in the preparation of anticholesterol ayurvedic formulation "Ayurslim", *Trigonella foenum-graecum* seeds have been used also(The Himalaya Drug Company, Bangalore, India) (Kumar, Bhandari, & Jamadagni, 2014).

2.2 Suspension

Suspension can be defined as a dispersed system in which a finely divided solid is dispersed uniformly in a liquid dispersion medium (Nash, 1988). Suspensions can be classified as coarse or colloidal dispersion based on the size of the particles. Suspensions with a particle size greater than 1 μm are termed as coarse suspension whereas those below 1 μm are known as colloidal suspensions. The term pharmaceutical suspensions apply to those suspensions when the solid particles of the disperse phase are therapeutically active. Pharmaceutical suspensions can be broadly classified as parenteral suspensions, topical suspensions and oral suspensions (Martin, Patel, Parsons, & Smith, 1983).The reasons for the formulation of a pharmaceutical suspension are as follows:

- The drug is insoluble in the delivery vehicle
- To mask the bitter taste of drug
- To increase drug stability
- To achieve controlled/sustained release

2.2.1 Advantages of Suspension

The advantages of the suspensions are as follows:

a) It is the only choice if the drug is not soluble in water or poorly soluble.

b) Drugs incorporated in suspension exhibits a higher rate of bioavailability due to its large surface area, heading to higher dissolution rate (Aulton, 2013).

c) Suspensions can mask unpleasant taste and odor (Sushma, Kumar, Ajay, & Ruuchi, 2013).

d) Suspensions can improve stability of drugs such as in case of parenteral suspension as drug is present in solid form, Hydrolysis and oxidation can be prevented that leads to degradation of drug.

e) Moreover, controlled release drug formulation and first pass hepatic effect can be eliminated (Patel R. M., 2010).

2.2.2 Disadvantages of Suspension:

The disadvantages of the suspensions are as follows:

a) As suspension is a bulk formulation so in single dosing inaccuracy may occur.

b) Temperature of storage, sedimentation rate, flow properties etc. are factors on which drug dose depends.

c) Temperature of storage is essential to maintain the stability of suspension.

d) Upon storage cake formation may occur (Eraga, Iwuagwu, & Adikwu, 2014).

2.3 Gums and Mucilages

Gums are naturally occurring components in plants. Natural gums are polysaccharides consisting of multiple sugar units linked together to create large molecules (Tekade & Chaudhari, 2013). In water mucilage dissolves and form colloidal solutionsMucilage's have

various uses such as emulsifying agent, suspending agent, thickeners, binders, film formers etc. Newer sources are need to be explored with the growing industrial demand (Jani, Shah, Prajapati, & Jain, 2009). The difference between gum and mucilage is that gums are pathological products whereas mucilage's are physiological products. Examples of gums are Acacia, tragacanth, guar gum. Mucilage's are found in epidermal cells of leaves, in seed coats, roots, barks, and middle lamella. For example Leaves (senna), roots (marshmallow).

Table 2.1: Pharmacopoeial Specifications for Natural Gums and Mucilages

Excipient	Test	Pharmacopeia
Acacia	Microbial limit, ash values	USP, JP, PhEur
Alginic acid	Microbial limit, pH, loss on drying	USP, PhEur
Carrageenan	Solubility, viscosity, loss on drying, ash value	USP
Dextrin	Loss on drying, residue on ignition, reducing sugars	USP, BP, JP
Gelatin	Isoelectric point, microbial limit, residue on ignition, loss on drying, total ash, jelly strength	USP, JP, PhEur
Guar gum	pH, microbial contamination, apparent viscosity, loss on drying, ash, galactomannans, organic volatile impurities	USP, PhEur
Lecithin	Water, arsenic, lead, acid value, heavy metals	USP
	Microbial limit, appearance of solution,	USP, PhEur

Sodium Alginate	loss on drying, ash, heavy metals	
Tragacanth	Microbial limits, flow time, lead, acacia and other soluble gums, heavy metals	USP, JP, PhEur
Xanthan gum	pH, viscosity, microbial limits, loss on drying, ash, heavy metals, organic volatile impurities	USP, PhEur

Table 2.2: Pharmaceutical Applications of Natural Gums and Mucilages

Common name	Botanical name	Family	Pharmaceutical applications	Reference
Albizia gum	Albizia zygia	Leguminosae	Tablet binder	(Ofoefule & Chukwu, 2001) (Odeku O. A., 2005)
Asario Mucilage	Lepidum Sativum	Cruciferae	Suspending agent emulsifying agent,	(Jain, Jani, Patel, Vithalani, & Shah, 2007) (Avachat & Dhamne)
Bavchi Mucilage	Ocimum Canum	Labiatae	Suspending agent, emulsifying agent	(Patel, Chauhan, & Patel, 1987)
Cashew gum	Anacardium occidentale	Anacardiaceae	Suspending agent	(Jaber & Ghazawi, 2005) (Bonferoni, Rossi, Pedraz, & Dominguez, 1994) (Pontes, 1971) (Zakaria & Zainiah, 1996)
Guar gum	Cyamompsis Tetraganolobus	Leguminosae	Binder,emulsifier disintegrant	(Pawar & D'Mello, 2004) (Gowthamrajan, Kulkarni, & Muthukumar, 2002) (Kulkarni, Gowthamrajan, & Muthukumar, 2002) (Kale,

				Kasliwal, & Parida, 2004) (Khullar, Khar, & Agarwal, 1998) (Heda & Shivhare, 2004)
Gum acacia	Acacia Arabica	Leguminoseae	Suspending agent, emulsifying agent, binder in tablets, demulcent and emollient	(Shefter E:Handbook of pharmaceutical excipients, 2009)
Gum ghatti	Anogeissus Latifolia	Combretaceae	Binder, Emulsifier. Suspending agent	(Jain & Dixit, 1988)
Gum Tragacanth	Astragalus Gummifer	Leguminosae	Suspending agent, emulsifying agent, Demulcent, emollient	(Handbook of pharmaceutical excipients, 2009)
Karaya gum	Sterculiaurens	Sterculiaceae	Suspending agent, emulsifying agent, dental adhesive, sustaining agent	(Sharma V. D., 1985) (Wahi & Jain, 1985) (Edwin, Edwin, & Dosi, 2007)
Khaya gum	Khaya grandifolia	Meliaceae	Binding agent	(Odeku & Itiola, 2003)

Sodium alginate	Macrocytis pyrifera	Lessoniaceae	Suspending and sustained release agent	(Razdan & Verma, 2003) (Verma, 2002) (Anroop, Bhatnagar, & Ghosh, 2005) (www.cpkelco.com/pectin/applications.html) (http://www,ippa.info/applications_for_pectin.html) (Kulkarni, Gowthamrajan, & Rao, 2002) (Howard & Timmins) (Seiyaku)
Xanthan gum	Xanthomonas lempestris -		Suspending agent, emulsifier, stabilizer	(Thierry, George, & John) (Kulkarni, Dwivedi, & Sarin, 1997) (Dhopeshwarkar & Zatz, 1993)
Gellan gum	Pseudomonas elodea -		Disintegrating agent	(Antony & Sanghavi, 1997)

Table 2.3: Applications of Natural Gums and Mucilage's in Novel Drug Delivery Systems

Common Name	Botanical Name	Family	Pharmaceutical Applications	Reference
Acacia	Acacia Senegal	Leguminosae	Osmotic drug delivery	(Beneke C. E., Viljoen, Viljoen, & Hamman, 2009)
Bhara gum	Terminalia bellericaroxb	Combretaceae	Microencapsulation	(Shankar, Nayak, Balakrishna, & Kumar, 2008)
Chitosan			Colon specific drug delivery, microspheres	(Wang, Xiong, & Lian, 2007)
Cordia gum	Cordia oblique willed	Boraginaecae	Oral sustained release matrix tablets	(Mukherjee, Dinda, & Barik, 2008)
Guar gum	Cyamompsis	Leguminoseae	Colon targeted drug	(Cardenus, Ciapara, &

	Tetraganolobus		delivery, microspheres	Goycoolea, 1997) (Krishnaiah, 2003) (Chourasia & Jain, Potential of Guar Gum Microspheres for Target Specific Drug Release to Colon, 2004)
Gellan gum	Pseudomonas elodea		Ophthalmic drug delivery, sustaining agents beads, hydrogels,	(Miyazaki, Kawasaki, Kubo, Endo, & Attwood, 2001) (Coviello, Dentini, & Rambone, 1998) (Agnihotri, Jawalkar, & Aminabhvi, 2006)
Karaya gum	Sterculiaurens	Sterculiaceae	Mucoadhesive and Buccoadhesive	(Alur, Pather, & Mitra, 1999) (Chourasia & Jain, Pharmaceutical approaches to colon targeted drug delivery systems., 2003) (Chavanpatil, Jain, & Chaudhari, 2006) (Park & Munday, 2004)
Locust bean gum	Cerataniasiliqua	Leguminoseae	Controlled delivery	(Xiaohong, Michae, & John, 2003)
Mucuna gum	Mucunaflagillepes	Papillionaceae	Microspheres	(Anthony & Nwabunze, 2007)
Okra gum	Hibiscus esculentus	Malvaceae	Hydrophilic matrix for controlled release drug delivery	(Kalu, Odeniyi, & Jaiyeoba, 2007)
Sodium alginate	Macrocytis pyrifera	Lessoniaceae	Bioadhvesive microspheres,	(Pornsak, Srisagul, & Satit, 2007) (Sungthongjeen,

			nanoparticles	Pitaksuteepong, & Somsiri, 1999) (Giunchedi, Conte, & Chetoni, 1999) (Ying, Parkar, & Luo, 2000)
Xanthan gum	Xanthomonas lempestris		Pellets, controlled drug delivery system	(Datta & Bandyopadhyay, 2006) (Vendruscolo, Andreazza, & Ganter, 2005)

2.3.1 Advantages of gums and mucilages:

Advantages of natural gums and mucilage's in pharmaceutical sciences are as follows:

1. Biodegradable:

Living organisms produce naturally available biodegradable polymers which are a renewable source and they are accepted because of hardly any harmful effect on humans or environmental health (e.g., skin and eye irritation).

2. Biocompatible and non-toxic

Most of the plant materials are carbohydrates and are composed of repeating sugar (monosaccharide's) units so they are not toxic and are biocompatible.

3. Low cost

The derivatives from natural sources are always cheaper and the production cost also becomes affordable.

4. Environmental-friendly processing

Production processing are very simple and gums and mucilage's can be collected in different seasons in bulk quantity quite easily.

5. Local availability (especially in developing countries)

In developing countries, industries use gums widely and that is why government also promote production in such case which increases the availability of gums and mucilage's.

6. Better patient tolerance as well as public acceptance

Chances of harmful effect are lower compared to the synthetic ones, for example, PMMA, povidone etc.

7. Edible sources

Most gums and mucilage's are found from edible source (Bhosale & Osmani, 2014).

2.3.2 Disadvantages of gyms and mucilages:

There are some disadvantages associated with natural gums and mucilage's which are discussed below:

a) Microbial contamination: Chance of microbial contamination is due to the equilibrium moisture content present in the gums and mucilage's and as they are exposed to the external environment. Proper handling and preservative can avoid microbial contamination.

b) Batch to batch variation: Fixed quantities of ingredients are used in synthetic manufacturing while the production of gums and mucilage's is dependent on environmental and seasonal factors.

c) Uncontrolled rate of hydration: Rate of hydration is uncontrollable as natural materials are collected at different times, as well as there are differences in region, species, and climate conditions. So the percentage of chemical constituents present in a given material may vary.

d) Reduced viscosity on storage: Normally, when gums and mucilage's come into contact with water, increased viscosity is noticed but after storage reduced viscosity is seen (Alam & Parrott, 1971).

2.3.3 Classification

Gums and mucilage's are found in high quantities in varieties of plants, animals, seaweeds, fungi and other microbial sources in which they perform a number of structural and metabolic function. Plant sources provide the largest amounts of gums and mucilage's. The different available gums and mucilage's can be classified as follows:-

1. According to the charge

A. Non-ionic seed gums:

Guar, Locust bean, Tamarind, Xanthan, Amylose, Arabinans, Cellulose, Galactomannans.

B. Anionic gums:

Arabic, Karaya, Tragacant, Gellan, Agar, Algin, Carrageenans, Pectic acid.

2. According to the source

A. Marine origin/algal (seaweed) gums:

Agar, Carrageenans, Alginic acid, Laminarin.

B. Plant origin:

Shrubs/tree exudates

— Gum arabica, Gum ghatti, Gum karaya, Gum tragacanth, Khaya and Albiziagums.

Seed gums

— Guar gum, Locust bean gum, Starch, Amylose, Cellulose.

Extracts

— Pectin, Larch gum

Tuber and roots

— Potato starch.

C. Animal origin:

Chitin and Chitosan, Chondroitinsulfate, Hyaluronic acid.

D. Microbial origin (bacterial and fungal):

Xanthan, Dextran, Curdian, Pullulan, Zanflo, Emulsan, Baker's yeast glycan, Schizophyllan, Lentinan, Krestin, Scleroglucan.

3. Semi-synthetic

A. Starch derivatives

— Hetastarch, Starch Acetate, Starch Phosphates.

B. Cellulose derivatives

— Carboxy methyl cellulose (CMC), hydroxy ethylcellulose, hydroxypropylmethylcellulose (HPMC), Methylcellulose (MC), microcrystalline cellulose (MCC).

4. According to shape

A. Linear:

Algins, Amylose, Cellulose, Pectins

B. Branched:

a. Short branches

— Xanthan, Xylan, Galactomanan.

b. Branch-on-branch

— Amylopectin, Gum arabic, Tragacanth.

2.4 Natural Gums and Mucilage's used as pharmaceutical excipients:

Almond Gum:

The source of Almond gum is the tree *Prunus amygdalus* (family: Rosaceae) which is a water soluble gum extrudes from wounds on almond tree. Gum includes aldobionic acid, L-arabinose, L-galactose, D-mannose, etc. As almond gum contains different components so it has emulsifying, thickening, suspending, adhesive, glazing, and stabilizing properties (Choudhary & Pawar, 2014).

Neem Gum:

Neem gum is obtained from the trees of *Azadirachta indica* which belongs to (Family: Meliaceae). This gum contains mannose, glucosamine, arabinose, galactose, fucose, xylose,

and glucose. It has binding property and sustained release property (Soni, Kumari, & Raju, 2015).

Aloe Mucilage:

Aloe mucilage is obtained from the leaves of Aloe barbadensis (Family: Liliaceae). Aloe barbadensis miller mucilage and Povidone combination have been used as release retardant for making sustained release matrix tablets (Ahad, et al., 2010).

Cashew Gum:

Cashew gum is the exudate from the stem bark of Anacardium occidentale (Family: Anacardiaceae) which contains galactose, arabinose, rhamnose, glucose, glucuronic acid, and other sugar residues. During hydrolysis of the gum yields L-arabinose, L-rhamnose, D-galactose, and glucuronic acid Cashew gum was also studied for its binding property and gum was compared with acacia which revealed that the disintegration time of the tablet increased with increase in concentration of cashew gum (Akoto, et al., 2008).

Locust Bean Gum:

Locust bean gum is a high molecular weight (3, 10,000) hydro colloidal polysaccharide. It is derived from the endosperm of the seed of Ceratonia siliqua Linn (Family leguminosae) It has an application as a compression coat (Pekamwar , Kalyankar, & Jadhav, 2019).

Hibiscus Mucilage:

Hibiscus Mucilage of Malvaceae family is also known as the shoe-flower plant, China rose, and Chinese hibiscus Mucilage of Hibiscus rosasinensis. Contains L-rhamnose, D-galactose, D-galactouronic acid and D-glucuronic acid. This is used in sustained release tablets (Bhaskar & Nithya, 2012).

Grewia Gum:

Grewia gum (Family, Tiliaceae) is derived from the inner bark of an edible plant. Its bark and leaves contain mucilage. It has binding properties and film coating agent property (Akdowa, et al., 2014).

Gellan Gum: Gellan gum is a polysaccharide. It is produced by the bacterium Sphingomonas elodea (formerly Pseudomonas elodea). It is used as a disintegrating agent. Moreover aqueous solution of this gum form gel (Agnello, et al., 2017).

CHAPTER 3

MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1. Materials

The materials used for the study are listed in Table 3.1

Table 3.1 Materials used for the study

Serial no.	Materials
01.	Mortar and pestle
02.	Glass rod
03.	Filter paper
04.	Beaker
05.	Volumetric flask
06.	Measuring cylinder
07.	Filter funnel
08.	Aluminum foil paper
09.	Pipette pump and filler
10.	Test tube
11.	Test tube stand
12.	Plastic bottle 100ml

3.2. Reagents

The reagents used in the formulations of suspension and their sources are listed in Table 3.2

Table 3.2 Reagents used in the formulation of suspension

Serial no.	Name of the Chemical	Source
01.	*Trigonella foenum graecum* (Fenugreek seeds)	Bangladesh
02.	Paracetamol powder (Commercial Grade)	China
03.	Glycerol	Merck, Germany
04.	Methyl Paraben	Merck, Germany
05.	Propyl Paraben	Loba, India
06.	Raspberry Flavor	Bangladesh
07.	Raspberry red color	Famous, Spain
08.	Acetone GR Grade	Active Fine Chemicals, Bangladesh
09.	Sodium saccharine	Cucku, China
10.	0.1N HCL	Active Fine Chemicals, Bangladesh

11.	Purified water	Bangladesh

3.3. Equipments

All the equipments used throughout the study are listed in Table 3.3

Table 3.3 Equipments used throughout the study

Name of the Equipment	Model	Manufacturer	Country of Origin
01. Electronic Balance 3-Digit	PA-213	Ohaus Corp	USA
02. Sieve shaker	EMS-8	ELECTROLAB	India
03.Digital pH Meter Benchtop	HI2211	HANNA Instruments	Italy
04. Viscometer	VISCO-88	Malvan Instruments Ltd.	United Kingdom
05. Water Bath (Six holes)	B120-DE	OVAN	EU
06. Dissolution Machine (8 Vessel	UDT-804	LOGAN instruments Corp	USA
07. UV-Spectrophotometer with PC	U-2910	HITACHI	Japan

Figure 3.1: Electronic Balance

Figure 3.2: Sieve shaker

Figure 3.3: Digital pH Meter

Figure 3.4: Viscometer

Figure 3.5: Water Bath

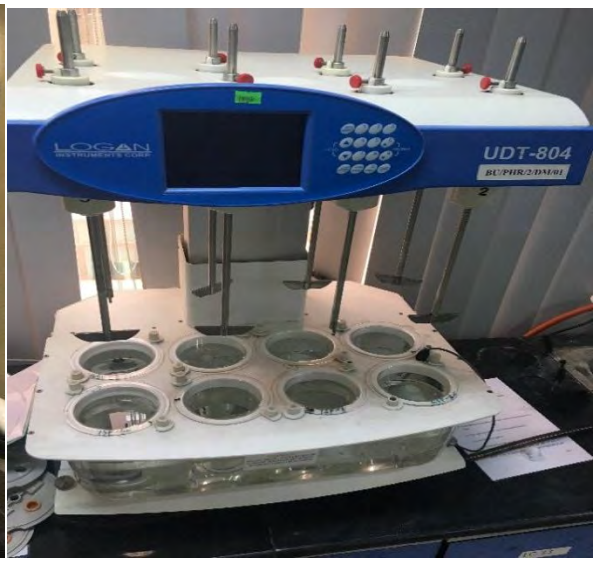


Figure 3.6: Dissolution Machine

Figure 3.7: UV-Spectrophotometer with PC

3.4 Methods

3.4.1 Extraction of suspending agent from *Trigonella foeneum graecum* (fenugreek seeds)

Initially seeds of *Trigonella foenum graecum* (fenugreek) were crushed in mortar and pestle and reduced in size. The crushed seeds were soaked in distilled water for 12 hours and boiled in water bath to prepare a slurry. Then the slurry was cooled and the unwanted material was allowed to settle down. Upper portion was collected and concentrated in water bath. After cooling the preparation, acetone was added to it with continuous stirring. Then the precipitate was collected and dried at room temperature for 24 hours. The air dried material was further subjected to size reduction using mortar and pestle and passed through

sieves (mesh size # 60) and sieved portion was used as a suspending agent for formulation of suspension.

3.4.2 Formulation of Suspensions

Five paracetamol suspension formulations (each of 100 ml) were prepared using varying proportions of *Trigonella foenum graecum* mucilage. The amount of each excipient used in the formulations is listed in Table 3.4.

Ingredients	FS1	FS2	FS3	FS4	FS5
Paracetamol (g)	2.5	2.5	2.5	2.5	2.5
Mucilage (g)	0.5	1	1.5	2	2.5
Glycerin (ml)	15	15	15	15	15
Sodium propyl paraben (g)	0.02	0.02	0.02	0.02	0.5
Sodium methyl paraben (g)	0.2	0.2	0.2	0.2	1
Sodium sachharin (g)	0.1	0.1	0.1	0.1	1
Flavour	q.s	q.s	q.s	q.s	q.s
Colour	q.s	q.s	q.s	q.s	q.s
Purified Water (up to 100 ml)	q.s	q.s	q.s	q.s	q.s

3.4.3 Evaluation of suspensions

The suspension formulations were evaluated using the following parameters.

3.4.3.1 pH determination of suspension

The pH of all the prepared formulations was measured using a digital pH meter (Model HI2211, HANNA Instruments, Italy).

3.4.3.2 Sedimentation volume

Sedimentation volume is determined by the following equation.

F=Hu/Ho

Where, Hu is ultimate or final height of sediment as suspension settles and Ho is original height of suspension.

3.4.3.3 Degree of Flocculation

Degree of flocculation (β) was determined using following equation:

$$\beta = \frac{(Vu)\ floc}{(Vu)\ defloc}$$

Where (Vu) floc is ultimate sedimentation volume of flocculated suspension and (Vu) defloc is ultimate sedimentation volume of deflocculated suspension.

3.4.3.4 Redispersibility

Fixed volume of each suspension (50 ml) was kept in test tubes which were stored at room temperature for various time intervals (1, 5, 10, 15, 20 days). At regular interval one tube was removed and shaken vigorously to redistribute the sediment and the presence of deposit (if any) was recorded.

3.4.3.5 Flow rate (F)

The time taken for 10 ml sample of suspension to flow through a 10 ml pipette was determined and the flow rate was calculated using the following equation:

F=Volume of pipette (ml)/Flow time (sec)

3.4.3.6 Determination of viscosity

The viscosity of suspension samples was determined using the Brookfield viscometer at 135 rpm. All the measurements were carried out in triplicates and results obtained were expressed as the mean values.

3.4.3.7. Effect of temperature

The effect of the temperature from 30º to 60º C was carried out on the viscosity of the suspension of all the formulations.

3.4.3.8 *In vitro* dissolution study

A standard curve of paracetamol was constructed by preparing solutions of various concentration of pure paracetamol drug (2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml). Absorbance of each prepared solution was measured at 273nm using double beam UV visible spectrophotometer and recorded. A plot of absorbance versus concentration (standard curve) was plotted using Microsoft Excel (Figure 3.8).

Dissolution study of formulated suspensions was carried out in USP type II dissolution test apparatus in 500 ml of 0.1N HCL for 20 min (37 º C ± 0.50 º C and 25rpm. 10 ml suspension was introduced carefully into the bottom of the apparatus. 5 ml aliquots were withdrawn at interval of 5 min for analysis and replenished by equivalent amount of blank. The aliquots were filtered through Whatman filter paper and further analyzed at 273nm by double beam UV visible spectrophotometer and the absorbance was measured. The parameters used for the dissolution study are listed in Table 3.5

Dissolution media	0.1 N HCL
Apparatus	Dissolution machine (USP Type II apparatus)
Stirring speed	25 rpm
Time	20 minutes
Temperature	37°C ± 0.5°C

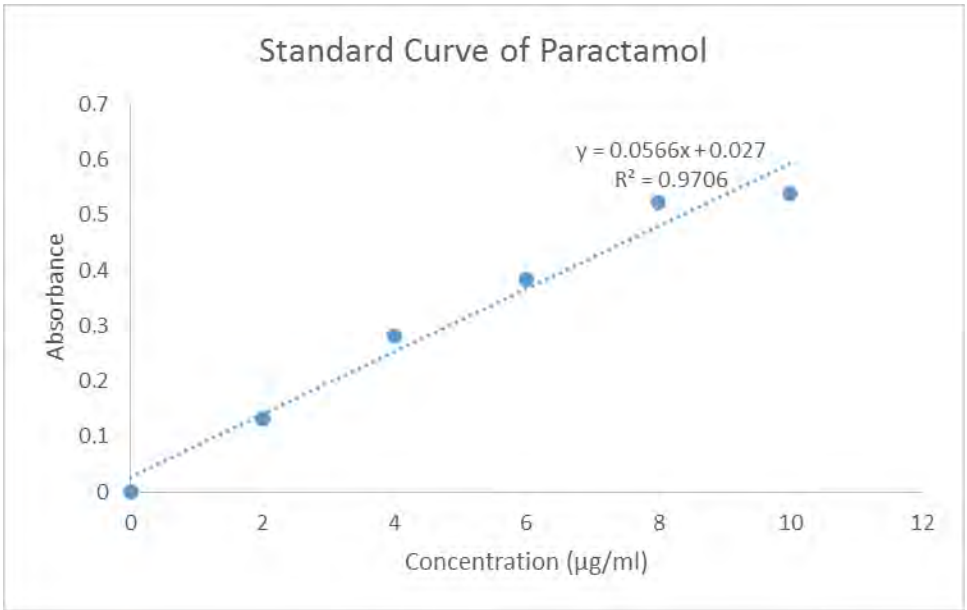


Figure 3.8: Standard Curve of Pure Paracetamol Drug

CHAPTER 4

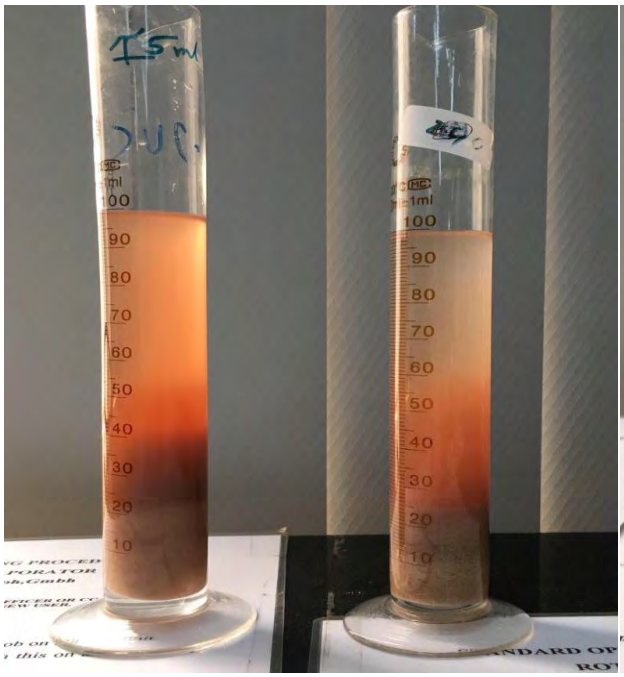
RESULTS AND DISCUSSIONS

4. RESULTS AND DISCUSSION

4.1 Physical Appearance

All the formulated paracetamol suspensions appeared cloudy and heterogeneous. Mucilage of *Trigonella Foenum Graecum* (fenugreek) was used as the suspending agent which was responsible for the initial greenish color of the suspensions. The final appearance of the

formulated suspension was dark pink in color owing to the raspberry color which was used to hinder the greenish color of the mucilage and to give the suspensions an improved better look for aesthetic appeal.



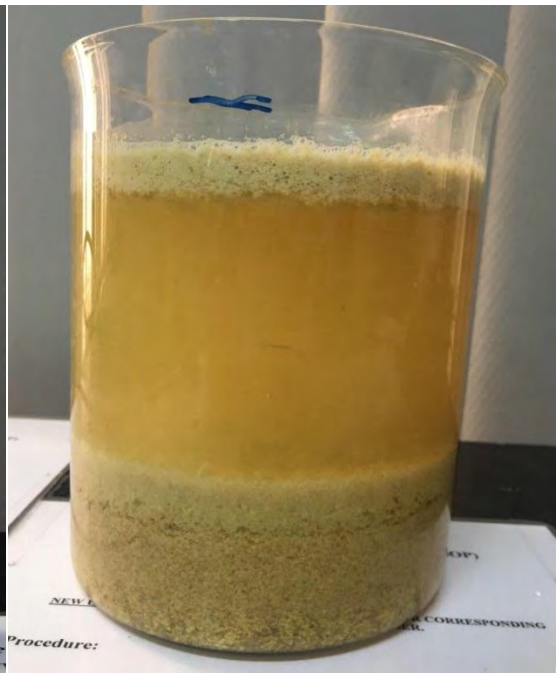


Figure 4.1: Acetaminophen Suspension **Figure4.2: Fenugreek seed mucilage**

4.2 Evaluation of suspension

All the formulated suspension designated as FS1, FS2, FS3, FS4 and FS5 were evaluated using the following parameters.

4.2.1 pH

pH of the FS1, FS2, FS3, FS4, FS5 formulated suspension was measured in triplicates. The results are shown in Table 1 and Figure 1. The pH values of the formulations ranged in between 7.5-7.9 except for formulation F5 which showed a greater pH value (pH 8.43) and also has a higher percentage of *Trigonella Foenum Graecum*.

Table 4.1: pH Values of the formulations

Formulation	% of *Trigonella*	pH values

Name	*Foenum Graecum* mucilage	1	2	3	Average± S.D
FS1	0.5g	7.91	7.90	7.91	7.90 ±0.01
FS2	1g	7.86	7.90	7.89	7.88 ±0.02
FS3	1.5g	7.48	7.47	7.46	7.47 ±0.01
FS4	2g	7.75	7.78	7.76	7.76 ±0.01
FS5	2.5g	8.42	8.43	8.45	8.43 ±0.01

Note: SD means Standard deviation

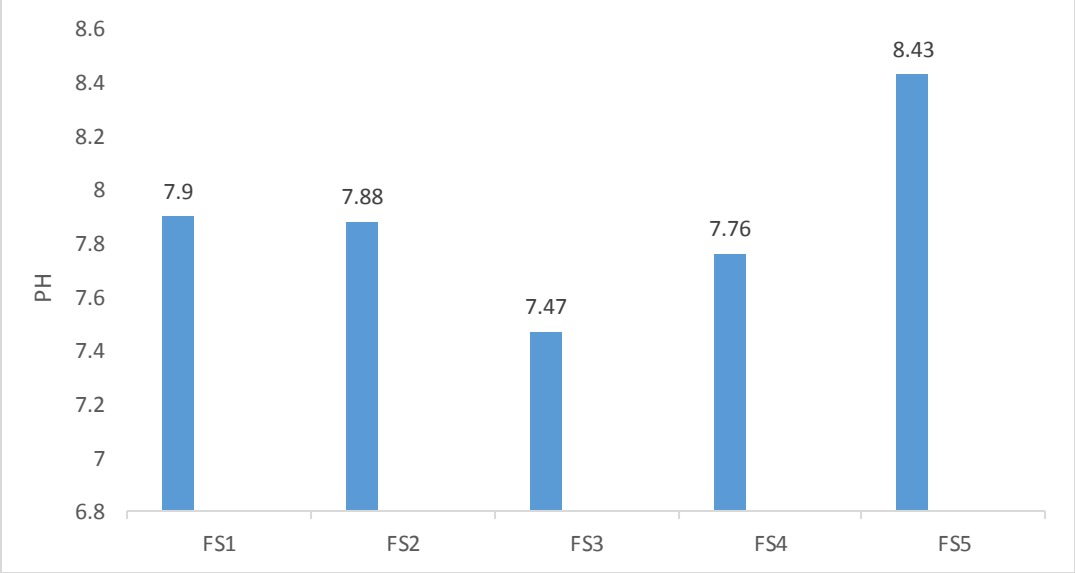


Figure 4.1: Comparative pH value for all formulated suspensions (FS1-FS5)

4.2.2 Sedimentation Volume

Sedimentation means settling of particle or floccules occur under gravitational force in liquid dosage forms. Sedimentation volume is the ratio of the height of the sediment after

settling and initial height of sedimentation (Sushma, Kumar, Ajay, & Ruuchi, 2013). The difference in sedimentation volume for all the suspension is shown in Table 4.2 and Figure 4.2. The sedimentation volume was found to increase with increase in percentage of the suspending agent *Trigonella foenum graecum* employed in the formulation. The sedimentation volume was also observed after 7 and 10 days from the day the suspensions were prepared. It was observed at the end of 7 and 10 days the sedimentation volume did not change significantly. Even, after 45 days, the sedimentation volume remained almost the same. Greater the sedimentation volume, lower the rate of sedimentation and greater the stability of the suspensions.

Table 4.2: Sedimentation Volume of the formulations

Formulation Name	% of TFG mucilage	Sedimentation Volume (Day 1)	Sedimentation Volume (Day 7)	Sedimentation Volume (Day10)	Sedimentation Volume (Day 45)
FS1	0.5g	0.12	0.09	0.07	0.06
FS2	1g	0.18	0.17	0.15	0.14
FS3	1.5g	0.17	0.14	0.12	0.12
FS4	2g	0.38	0.22	0.22	0.21
FS5	2.5g	0.68	0.60	0.58	0.53

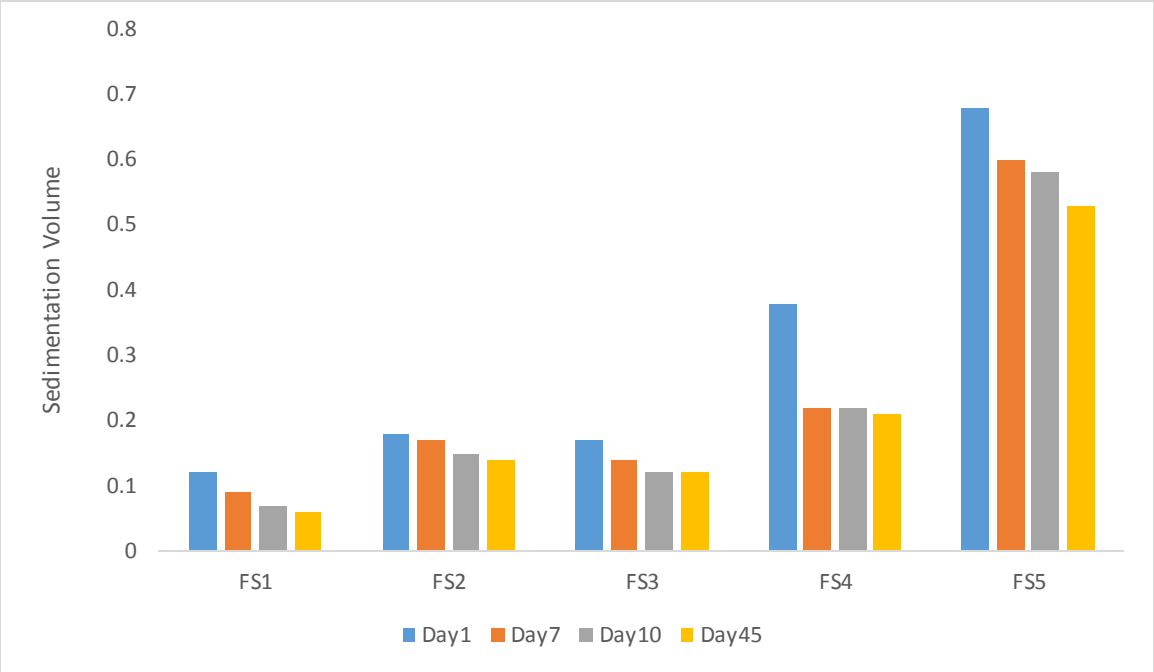


Figure: 4.2 Sedimentation Volume of the formulations

4.2.3 Degree of flocculation:

Degree of flocculation (β) is a parameter for comparing flocculated systems which relates the sedimentation volume of the flocculated suspension (F) to the sedimentation volume of the suspension when deflocculated (F_∞). The degree of flocculation is determined by dividing the sedimentation volume of flocculated suspension (F) to the sedimentation volume of the suspension when deflocculated (F_∞) (Remington : the science and practice of pharmacy., 2006).The value of the sedimentation volume of the deflocculated suspension is 0.02. The results of the degree of flocculation on day 1, 7, 10 and 45 are tabulated in Table 4.3. From the values, it can be seen that the degree of flocculation for all the formulations decreases with time but not significantly showing greater stability of the suspensions. Suspensions with a higher proportion of suspending agent exhibits a higher degree of flocculation (degree of flocculation for formulation FS1 with 0.5 gm of suspending agent is 6.66 whereas for FS 4 and FS 5 with 2 gm and 2.5 gm of suspending agent respectively has degree of flocculation values 21.11 and 37.77 respectively). Higher degree of flocculation is

a desirable property of the suspension formulations as it expresses increased sediment volume and thus there will be minimum settling of the drug particles and will prevent cake formation.

Table: 4.3 Degree of flocculation of formulated suspension

Formulation Name	% of *Trigonella Foenum Graecum* mucilage	Degree of Flocculation Day 1	Degree of Flocculation Day 7	Degree of Flocculation Day 10	Degree of Flocculation Day 45
FS1	0.5	6.66	5.29	4.11	4
FS2	1	10	10	8.82	8.33
FS3	1.5	9.44	8.23	7.05	7.01
FS4	2	21.11	20.94	20.94	19.8
FS5	2.5	37.77	35.29	34.11	33.1

4.2.4 Viscosity

Viscosity is a fluid's resistance to flow. It can also be defined as the amount of force required to get that substance moving. It is the force per unit area, so viscosity is equal to force divided by area (Mastropietro, NImroozi, & Omidian, 2013). In FS1 formulation the average viscosity value was 0.026 P (poise) at speed 7 (572 rpm). For FS2, FS3, FS4 formulation the average viscosity value was 0.032, 0.036, 0.043 P (poise) at speed 6 (327 rpm), speed 7 (572 rpm), speed 6 (37 rpm) respectively. Finally in the case of FS5 viscosity value was 0.124 P (poise) at speed 5 (187 rpm) which shows that the value of viscosity was found to increase with increase in percentage of the suspending agent *Trigonella foenum graecum* used in the formulation. Greater the percentage of the suspending agent used, greater will be the viscosity of the suspension thus producing flocculated and more stable suspensions.

Table 4.4: Viscosity values of the formulations

Formulation Name	% of *Trigonella foenum graecum* mucilage		Viscosity Poise (P)			
		Speed	1	2	3	Average ± S.D
FS1	0.5g	Speed 7	0.027	0.026	0.027	0.026±0.00
FS2	1g	Speed 6	0.032	0.031	0.032	0.031±0.00
FS3	1.5g	Speed 7	0.036	0.037	0.035	0.036±0.000
FS4	2g	Speed 6	0.044	0.043	0.042	0.043±0.00
FS5	2.5g	Speed 5	0.124	0.124	0.124	0.123±0.00

Note: Speed 7: 572 rpm

Speed 6: 327 rpm

Speed 5: 187 rpm

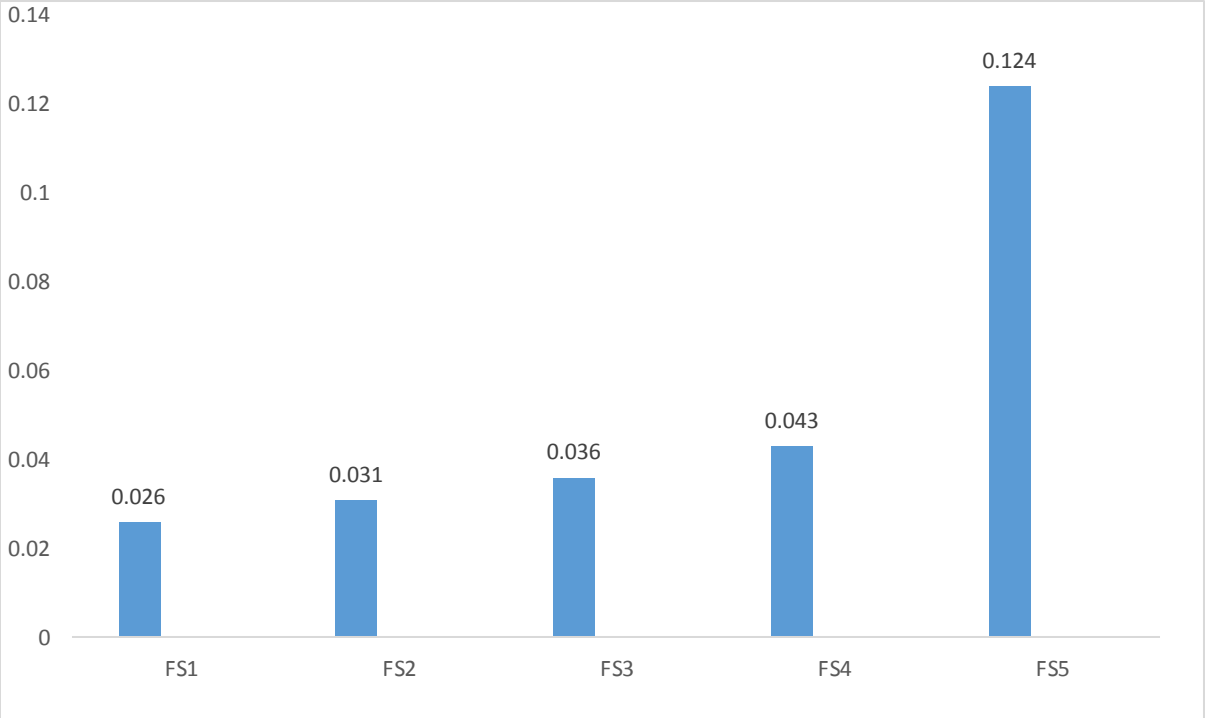


Figure 4.4: Comparative Viscosity value for all formulated Suspensions

4.2.5 Redispersibility

The ease with which a suspension redisperses after shaking is a measure of the suspensions physical stability. The redispersibility test was done at day 1, 7, 10 and after 45 days. With the lower percentage of *Trigonella foenum Graecum* mucilage such as FS1 formulation, on an average 2 shakes were enough to redisperse the suspension entirely whereas with the higher percentage of *Trigonella Foenum Graecum* mucilage, at least 4 shakes was required to redisperse fully. It must be noted due to higher percentage of suspending agent, it was expected that greater number of shaking times would be required to redisperse the suspension formulation but these did not need to be shaken as many times as expected as they were in a flocculated state already. From the redispersibility results, it is evident that that suspensions formulated have good physical stability.

Table 4.5: Redispersibility of the formulations

Formulation Name	% of *Trigonella Foenum Graecum* mucilage	Redispersibility (Day 1)	Redispersibility (Day 7)	Redispersibility (Day 10)	Redispersibility (Day 45)
FS1	0.5g	Easily Redispersable After shaking 2 times	Easily Redispersable After shaking 2 times	Easily Redispersable After shaking 3 times	Easily Redispersable After shaking 3 times
FS2	1g	Easily Redispersable After shaking 2 times	Easily Redispersable After shaking 2 times	Easily Redispersable After shaking 3 times	Easily Redispersable After shaking 3 times
FS3	1.5g	Easily Redispersable After shaking 2 times	Easily Redispersable After shaking 2 times	Easily Redispersable After shaking 3 times	Easily Redispersable After shaking 3 times
FS4	2g	Easily Redispersable After shaking 3 times	Easily Redispersable After shaking 3 times	Easily Redispersable After shaking 4 times	Easily Redispersable After shaking 4 times
FS5	2.5g	Easily Redispersable After shaking 3 times	Easily Redispersable After shaking 3 times	Easily Redispersable After shaking 4 times	Easily Redispersable After shaking 4 times

4.2.6 Flow rate

The rate of flow of the suspension through the 10 ml pipette is an estimate of the ease with which the suspension will be poured from the packaged bottle. The results of the values of flow rate is recorded in Table 4.6 and shown in Figure 4.6. The flow rate of the suspension decreased with increase in concentration of suspending agent since as expected. Suspending agents increase the viscosity of the formulated suspension and thus it took more time for the suspensions with higher proportion of *Trigonella Foenum Graecum* to flow through 10 ml pipette. However, no difference in flow rate was observed for formulation FS3 and FS4 (both formulation has an average value of 1.5 ml/sec) suggesting that 2 gm of *Trigonella Foenum Graecum* can be used instead of 1.5 gm of *Trigonella Foenum Graecum* in order to prepare a more stable flocculated suspension.

Table 4.6: Flow rate of the formulations

Formulation Name	% of TFG mucilage	Flow rate (volume of pipette/Time) (ml/s)			Average± S.D
FS1	0.5g	1.11	1.11	1.12	1.11±0.00
FS2	1g	1.21	1.22	1.22	1.21±0.00
FS3	1.5g	1.50	1.51	1.52	1.51±0.00
FS4	2g	1.50	1.52	1.52	1.51±0.00
FS5	2.5g	0.40	0.41	0.42	0.41±0.00

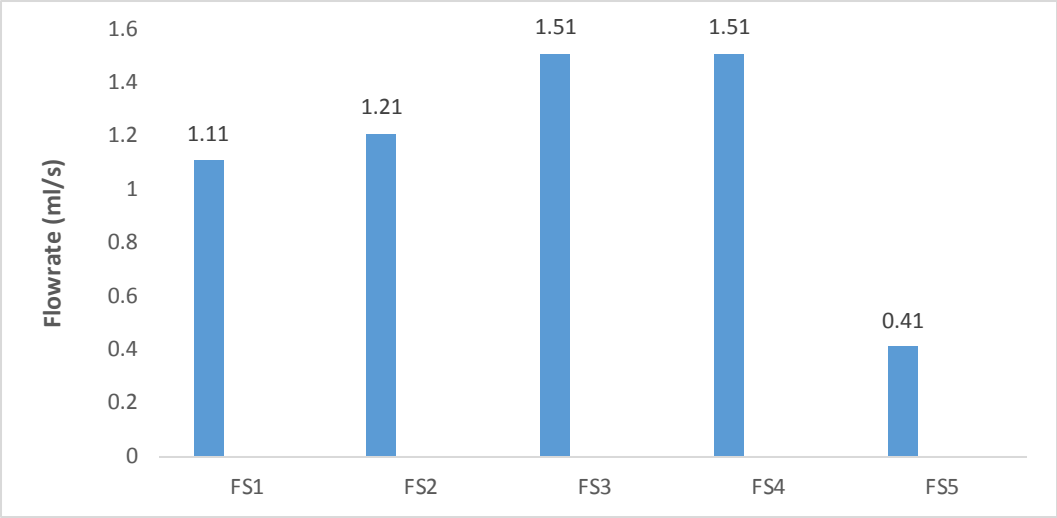


Figure 4.6: Comparative Flow rate values for all the formulated Suspensions

4.2.7 Effect of Temperature on Viscosity

The increase in temperature of the formulated suspension reduced the viscosity of the formulated suspensions. For example, in case of FS1 formulation, increase in temperature from 30º C to 60ºC decreased the viscosity of the suspension (at 30° C the average viscosity value is 0.095 and at 60° C the average viscosity value decreased to 0.074) . Overall, all the formulated suspensions showed same property as shown in Table 4.7.

Table 4.7. Effect of Temperature on Viscosity

Formulation Name	% of *Trigonella foenum Graecum* mucilage	Speed	Effect of Temperature on Viscosity [P = poise]			
			30 ° C	40 ° C	50 ° C	60 ° C
FS1	0.5g	Speed 7	0.094 0.095 0.096	0.080 0.081 0.082	0.078 0.079 0.078	0.072 0.079 0.070
FS2	1g	Speed 6	0.132 0.133 0.134	0.131 0.132 0.134	0.131 0.131 0.133	0.130 0.130 0.131
FS3	1.5g	Speed 7	0.170 0.171 0.170	0.169 0.170 0.169	0.165 0.165 0.163	0.164 0.164 0.160
FS4	2g	Speed 6	0.372 0.371 0.370	0.370 0.369 0.370	0.360 0.368 0.369	0.358 0.361 0.367
FS5	2.5g	Speed 5	0.101 0.102 0.103	0.101 0.103 0.102	0.100 0.101 0.100	0.100 0.100 0.100

4.2.8 Dissolution study

Determination of *in vitro* dissolution rate of a drug from a dosage form is imperative for the design and development of an optimum formulation and subsequently for bioequivalence

studies. The percentage release of drug from the formulated paracetamol suspensions was carried out in USP type II dissolution test apparatus in 500 ml of 0.1N HCL for 20 minutes.

Although mainly designed for tablets and capsules, this apparatus has been used in several studies to comprehend the dissolution behavior of suspensions. (Strum, et al., 1978) (Hashem & El-Said, 1987) (Abdou, 1995) There is no official specification mentioned as a minimum limit for dissolution of paracetamol suspensions within a specified period of time. However, according to USP specifications not less than 80% is accepted within 30 minutes for tablets. (Rockvilli, 1990)In this regard, the dissolution of the suspensions were found to be satisfactory since as on an average 65-70% of the drug was released within 20 minutes even at a slow speed of 25 rpm as shown in the following tables (Table 4.8, 4.9, 4.10, 4.11, 4.12).

Table 4.8. Dissolution study of FS1 Suspension

FS1 Suspension with 0.5gm *Trigonella Foenum Graecum* mucilage										
Time (Minute)	**Absorbance (y)**							**Concentration (x)**	**Amount Released (mg)**	**Percent of drug release (%)**
	1	**2**	**3**	**4**	**5**	**6**	**Avg**			
5	0.082	0.081	0.08	0.089	0.074	0.038	0.074	0.83	83	33.2
10	0.052	0.051	0.05	0.062	0.05	0.052	0.053	0.45	45	18
15	0.041	0.041	0.045	0.048	0.046	0.05	0.045	0.31	31	12.4
20	0.041	0.042	0.038	0.036	0.04	0.041	0.040	0.22	22	8.8

Table 4.9: Dissolution study of FS2 Suspension

FS2 Suspension with 1 gm *Trigonella Foenum Graecum* mucilage

Time (Minute)	Absorbance (y)							Concentration (x)	Amount Released (mg)	Percent of drug release (%)
	1	2	3	4	5	6	Avg			
5	0.08	0.078	0.079	0.07	0.076	0.036	0.070	0.75	75	30
10	0.051	0.052	0.052	0.06	0.058	0.055	0.055	0.49	49	19.6
15	0.041	0.041	0.045	0.041	0.046	0.049	0.044	0.3	30	12
20	0.038	0.036	0.045	0.048	0.038	0.041	0.041	0.24	24	9.6

Table 4.10: Dissolution study of FS3 Suspension

FS3 Suspension with 1.5 gm *Trigonella Foenum Graecum* mucilage										
Time (Minute)	Absorbance (y)							Concentration (x)	Amount Released (µg)	Percent of drug release (%)
	1	2	3	4	5	6	Avg			
5	0.071	0.072	0.071	0.079	0.074	0.031	0.066	0.68	68	27.2
10	0.042	0.041	0.052	0.058	0.054	0.05	0.050	0.4	40	16
15	0.045	0.041	0.041	0.041	0.049	0.046	0.044	0.3	30	12
20	0.039	0.035	0.046	0.049	0.041	0.042	0.042	0.26	26	10.4

Table 4.11: Dissolution study of FS4 Suspension

FS4 Suspension with 2.0 gm *Trigonella Foenum Graecum* mucilage										
Time (Minute)	**Absorbance (y)**							**Concentration (x)**	**Amount Released (mg)**	**Percent of drug release (%)**
	1	**2**	**3**	**4**	**5**	**6**	**Avg**			
5	0.069	0.065	0.067	0.061	0.064	0.063	0.065	0.67	67	26.8
10	0.043	0.04	0.05	0.054	0.051	0.051	0.048	0.37	37	14.8
15	0.041	0.047	0.042	0.039	0.046	0.049	0.044	0.3	30	12
20	0.04	0.037	0.036	0.035	0.041	0.036	0.038	0.19	19	7.6

Table 4.12: Dissolution study of FS5 Suspension

FS5 Suspension with 2.5 gm *Trigonella Foenum Graecum* mucilage										
Time (Minute)	**Absorbance (y)**							**Concentration (x)**	**Amount Released (mg)**	**Percent of drug release (%)**
	1	**2**	**3**	**4**	**5**	**6**	**Avg**			
5	0.074	0.072	0.077	0.071	0.069	0.07	0.072	0.79	79	31.6
10	0.043	0.043	0.051	0.051	0.052	0.049	0.048	0.37	37	14.8
15	0.041	0.044	0.052	0.043	0.044	0.048	0.045	0.31	31	12.4
20	0.049	0.04	0.042	0.048	0.041	0.036	0.043	0.26	26	10.4

The present study also revealed that the dissolution rate may be related to the viscosity of the suspensions. The viscosity of the suspensions formulated increased with increase in the concentration of the suspending agent used which in turn decreased the dissolution rate of the suspensions. As for example, the percentage release of drug for FS1 Suspension with 0.5gm *Trigonella Foenum Graecum* mucilage after 5 minutes is 33.2% whereas for FS4

Suspension with 2.0 gm *Trigonella Foenum Graecum* mucilage, it was found to be 26.8%. However, a completely different scenario was observed for FS5 Suspension with 2.5 gm *Trigonella Foenum Graecum* mucilage that showed a percentage release of drug of 31.6% thus showing that decrease in viscosity didn't attribute to a decrease in its dissolution rate.

CHAPTER 5

CONCLUSION

Conclusion

The present study was aimed at utilizing *Trigonella foenum graceum* (Family: Leguminosae) seeds, also known as fenugreek seeds, as a suspending agent in pharmaceutical suspensions. Five suspension formulations designated as FS1, FS2, FS3, FS4 and FS 5 containing varying proportions of of *Trigonella foenum graceum* mucilage as the suspending agent (0.5g, 1g, 1.5g, 2g, 2.5g respectively) and acetaminophen as the active pharmaceutical ingredient were prepared and evaluated. The other excipients used were methyl paraben, propyl paraben, raspberry flavor and red colouring agent. The suspensions were subjected to evaluation by studying different parameters like pH, sedimentation volume, degree of flocculation, viscosity, redispersibility, flow rate, effect of temperature on viscosity and finally the rate of release of drug within twenty minutes. pH of all the formulations were found to be similar (approximately 7.8). The sedimentation volume did not change significantly over a period of 45 days indicating higher degree of flocculation and good stability of the suspensions. The suspensions were easily redispersible after shaking only twice even after 45 days and the flow rate of the suspensions did not differ much suggesting that suspensions with 2 gm of mucilage (FS4) can be used instead of FS3 (with 1.5 gm of mucilage) as it gives a higher degree of flocculation. The dissolution results of the suspensions were found to be satisfactory since on an average 65-70% of the drug was released within 20 minutes, thus complying with USP specifications. Even though all the formulations gave good results, it can be concluded that FS4 formulation is the optimum formulation with greater flocculation, good flow rate and easily redispersibility characteristics along with a good percentage release of drug within twenty minutes. The study reveals the potential of *Trigonella foenum graceum* mucilage as a natural suspending agent and these formulations should be compared with the market preparations for further evaluation.

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