

**FORMULATION AND EVALUATION OF ORO-DISPERSIBLE
PAEDIATRIC SILDENAFIL TABLETS USING JUTE PLANT
MUCILAGE**

By

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U53/81034/2015

**A Research Dissertation submitted in partial fulfillment of the Requirements for the
Award of the Degree of Master of Pharmacy in Industrial Pharmacy of the University of
Nairobi.**

2017

DECLARATION

This research work is my original work and has not been submitted anywhere for examination, award of a degree or publication.

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ACKNOWLEDGEMENTS

My heartfelt gratitude goes to the following:

Almighty God for the divine guidance and strength to successfully complete this work.

The Ministry of Health for awarding me the Post-graduate Studies' Scholarship.

My highly supportive and resourceful supervisor, Dr. Lucy J. Tirop, for the advice and guidance in the course of the study.

To the Chairperson Pharmaceutics and Pharmacy Department, Dr. Shital Maru, for facilitating and providing an enabling environment for the research, in spite of the challenges across the year.

To the Chairman Pharmaceutical Chemistry Department, Dr. Abuga K.O, for permission to use the facilities at Drug Analysis and Research Unit.

To the Director NQCL Dr. Hezekiah Chepkwony, the deputy director Dr. Mbae and R&D manager Dr. Mwaura for allowing me to use the facilities at the Laboratory, and providing the invaluable assistance with the analysis.

To the technical support staff; Raphael Ingwela, Mugo, Achoki and Agnes for the assistance and company throughout the project.

To my colleagues; Dr. Martha, Dr. Titus, Dr. Nicole and Dr. Chepkwony for your encouragement and company.

DEDICATION

To my loving husband Eric Mwai and son, Nathan Mwai, for the permission and moral support that facilitated completion of this research project.

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ABBREVIATIONS AND ACRONYMS

ANOVA	Analysis of Variance
AOR	Angle of Repose
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutics Classification System
CI	Carr's Index
cGMP	Cyclic Guanosine Monophosphate
CMS	Croscarmellose Sodium
CRP	Crospovidone
CSD	Colloidal Silicon Dioxide
FDA	Food and Drug Administration
FDTs	Fast Dispersible Tablets
HCl	Hydrochloric Acid
HR	Hausner's Ratio
IR	Infrared
MCC	Microcrystalline Cellulose
ODT	Oro-Dispersible Tablet
PAH	Pulmonary Arterial Hypertension

PDE	Phosphodiesterase
PPHN	Persistent Pulmonary Hypertension of the New-born
RSD	Relative Standard Deviation
SC	Sildenafil Citrate
SD	Standard Deviation
SSG	Sodium Starch Glycolate
USP	United States Pharmacopoeia
UV	Ultra Violet
WHO	World Health Organization

ABSTRACT

Sildenafil citrate a phosphodiesterase 5 inhibitor is a vasodilator used in the management of pulmonary arterial hypertension in both adults and children. In the latter, no dose specific formulation is locally available. Paediatric doses are prepared extemporaneously by splitting the adult dosage forms a process which is tedious and error prone. This work aimed to develop a convenient and dose specific oro-dispersible tablet of Sildenafil citrate for paediatric patients. Additionally, use of *Corchorus olitorius* mucilage as a novel natural superdisintegrant which is non-toxic and a nutritional supplement, would deliver a potentially superior oral dispersible tablet.

Mucilage of *Corchorus olitorius* jute plant was successfully extracted from its leaves and characterized. The high swelling index of 85.7% renders a great potential for its use as a superdisintegrant. For comparison purposes, common synthetic superdisintegrants, namely croscarmellose sodium, crospovidone and sodium starch glycolate were also used for tablet formulation. Twelve batches of tablets each containing 2.5 mg Sildenafil citrate were prepared whilst varying concentrations of each superdisintegrant. Drug excipient compatibility analysis of active pharmaceutical ingredient and all the excipients by infra-red spectroscopy revealed that there were no predictable drug-excipient interactions. The pre-compression studies on powder blends for Carr's Index and Hausner's Ratio demonstrated a passable flow character according to the United States Pharmacopoeia 29, hence the tablets were formulated by direct compression.

All the batches were evaluated for compendial quality attributes namely weight uniformity, tablet hardness, friability, thickness, wetting time, water absorption ratio, *in-vitro* dispersion time, assay and content uniformity. Tablet batches formulated with *Corchorus olitorius* mucilage were similar to the synthetic superdisintegrants batches in most of the attributes, with

characteristic mean in-vitro dispersion times of 20.67, 19.33 and 18.67 seconds for the 5 mg, 7.5 mg and 10 mg disintegrant concentrations respectively. *Corchorus olitorius* mucilage may thus be used as a superdisintegrant in oro-dispersible tablets.

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Sildenafil citrate (SC), a Phosphodiesterase 5 (PDE 5) inhibitor, is used in the management of pulmonary arterial hypertension (WHO Group 1) in both adults and children (1). It is available as tablets of 20mg, 25 mg, 50 mg and 100 mg strengths as well as an intravenous solution and oral suspension, Revatio[®], in the United States. Its mode of action is stimulation of pulmonary vasodilation through raising the levels of intracellular cyclic guanosine monophosphate (cGMP). The safety and efficacy of Sildenafil citrate for management of paediatric pulmonary arterial hypertension has been demonstrated, and the United States Food Drugs Administration (FDA) recommends its use given continued routine monitoring (2). Sildenafil citrate is useful in management of persistent pulmonary hypertension of the newborn (PPHN), although use in children under one year of age is off-label (3).

The dosing recommendation for SC in management of acute pulmonary hypertension in children below 1 year is a starting dose of 0.25-0.5 mg/kg *per oral* every 4 to 8 hours, and 2.5mg three times a day for those aged above 1 year, with a body weight below 20 kg (4). Due to lack of a dose specific dosage form, current practice in resource limited settings involves splitting the adult tablets and extemporaneous preparations of liquid dosage forms. The compounded liquid preparations are stable for 3 months, with or without preservatives, and should be refrigerated once opened and used within 14 days (5). Splitting tablets is based on the assumption that the active pharmaceutical ingredient (API) is uniformly distributed throughout the product, which is often not the case. Tablets are often difficult to cut and divide appropriately. Their palatability is

also reduced due to rough edges revealing the active drug's taste (6). There is need therefore of a dosage form that provides accurate dosage, to enhance efficacy and safety, one that is easy to produce and dispense, with minimal manipulation to reduce the risk of errors (7).

An oro-dispersible tablet is a highly convenient dosage form that takes into consideration swallowing difficulties especially among paediatrics, geriatrics, patients suffering from difficulties in swallowing, and repeated episodes of vomiting. This tablet disintegrates in the mouth within seconds thus easily swallowed in the absence of water, and very little or no residue is left upon being orally administered (8). There is potential pre-gastric absorption which eliminates pre-systemic metabolism of the drug (9). It provides rapid drug delivery with a very fast onset of action and increased bioavailability (10,11). Several conventional techniques for preparation of oro-dispersible tablets (ODTs) exist, which include: direct compression with use of superdisintegrants, spray-drying, lyophilisation, moulding, mass-extrusion, nanonization, compaction and sublimation. Some patented techniques include Zydis®, Orasolv®, Durasolv®, and Flashtab® (8).

Direct compression technique is preferred as it is simple, effective and economical (8). Superdisintegrants are added in optimal concentrations to achieve rapid disintegration. Superdisintegrants may be broadly classified as synthetic such as croscarmellose sodium, and natural (11). Natural superdisintegrants have been shown to exhibit faster drug dissolution and improved bioavailability of the API. They have mainly been sourced from plant mucilages and gums (12). Plants known to contain high concentrations of mucilage include: *Corchorus olitorius* leaves (Jute plant), *Trigonella foenum-graceum* seeds (Fenugreek), *Plantago ovata* (desert Indian wheat), *Lepidium sativum* (garden cress) and *Hibiscus rosa-sinensis* (13) .

Natural superdisintegrants have in various studies exhibited faster disintegration than the widely used synthetic superdisintegrants (12). For instance, in a comparative study carried out by Naazia zafar *et al.* on superdisintegrant activity of Fenugreek seed mucilage, against synthetic superdisintegrants and conventional disintegrants, the least disintegration time was observed with fenugreek seed mucilage (14). The natural superdisintegrants are also cheaper, biocompatible and biodegradable hence ecofriendly, easily available, non-toxic and have no side-effects (15).

The Jute plant, *Corchorus olitorius*, is grown in most parts of the country particularly Western Kenya and is a favourite indigenous leafy vegetable, 'mrenda', amongst the western Kenya communities. It is highly nutritious and very mucilaginous. It is therefore a potential source of a cheap, non-toxic and easily available natural superdisintegrant.

In this study, the superdisintegrant activity of mucilage from the Jute plant will be investigated, in the formulation of a 2.5 mg SC oro-dispersible tablet, for easy administration of the drug to paediatric pulmonary arterial hypertension patients.

1.2 PROBLEM STATEMENT

Sildenafil citrate has been demonstrated to be effective when administered orally in the management of pulmonary arterial hypertension (PAH) in adults and children (4). It is particularly useful for the management of persistent pulmonary hypertension of the newborn (PPHN) although use in children under the age of 1 year is off-label. There however lacks a suitable dosage form for children locally, with current practice involving splitting adult tablets into multiple pieces to achieve doses fit for children, and the tedious preparation of liquid

formulations extemporaneously. These liquid formulations have to be refrigerated once opened and are stable for up to 14 days. Splitting tablets is usually difficult and wasteful with the inherent risk of errors. There is therefore need for a suitable and convenient paediatric dosage form. A 2.5 mg SC oro-dispersible tablet will be dose specific and highly convenient for children.

Direct compression as a method of manufacture is effective and more economical as it eliminates the multiple processing steps and additional equipment necessary for wet or dry granulation. Superdisintegrants are incorporated as an integral component that ensures rapid disintegration through water absorption and swelling to achieve oral dispersion of the tablets. Natural superdisintegrants have been shown to exhibit faster disintegration than conventional disintegrants and synthetic superdisintegrants. They are also biocompatible, biodegradable, non-toxic and easily available. A locally available natural superdisintegrant would therefore aid in the reduction of the production cost while potentially delivering a superior ODT.

In this study, a 2.5mg sildenafil citrate oro-dispersible tablet will be formulated using synthetic superdisintegrants and *Corchorus olitorius* leaves mucilage to investigate and compare its superdisintegrant activity.

1.3 OBJECTIVES

1.3.1 General objective

The main objective of this study is to formulate a paediatric oro-dispersible tablet of sildenafil citrate, using mucilage from leaves of *Corchorus olitorius* (Jute plant).

1.3.2 Specific objectives

The specific aims for the study are:

- To extract mucilage powder from the leaves of *Corchorus olitorius* and evaluate its physicochemical characteristics.
- To conduct preliminary formulation studies on powder blend of sildenafil citrate and excipients.
- To formulate the oro-dispersible tablets of sildenafil citrate for paediatrics using the mucilage as well as synthetic superdisintegrants, and comparatively evaluate their physicochemical characteristics.

1.4 Significance and anticipated outcome

Sildenafil citrate is effective and safe in the management of pulmonary arterial hypertension (WHO group 1) in children (4). Lack of a dose specific formulation for this paediatric sub-population has led to the tedious and error prone practice of extemporaneous liquid preparations from adult dose tablets. The formulation of a 2.5 mg oro-dispersible Sildenafil citrate tablet will effectively address this challenge, while use of a natural superdisintegrant from mucilage of *Corchorus olitorius* leaves will minimize the associated production costs as well as potentially deliver a superior ODT.

CHAPTER 2: LITERATURE REVIEW

2.1 PHYSICOCHEMICAL PROPERTIES OF SILDENAFIL CITRATE

Sildenafil citrate (Figure 2.1) is a bitter-tasting, off-white crystalline powder, with a solubility of 3.5 mg/ml in water (9) . It is classified as a Biopharmaceutics Classification System class 1 compound (16). The chemical name and empirical formula of SC are 1-[3-(6, 7-dihydro-1-methyl-7-oxo-3-propyl)-1H-pyrazolo-{4, 3-d} pyrimidin-5-yl)-4-ethoxyphenyl]-sulphonyl-4-methylpiperazine citrate and $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ respectively. It has a molecular weight of 666.71 (17).

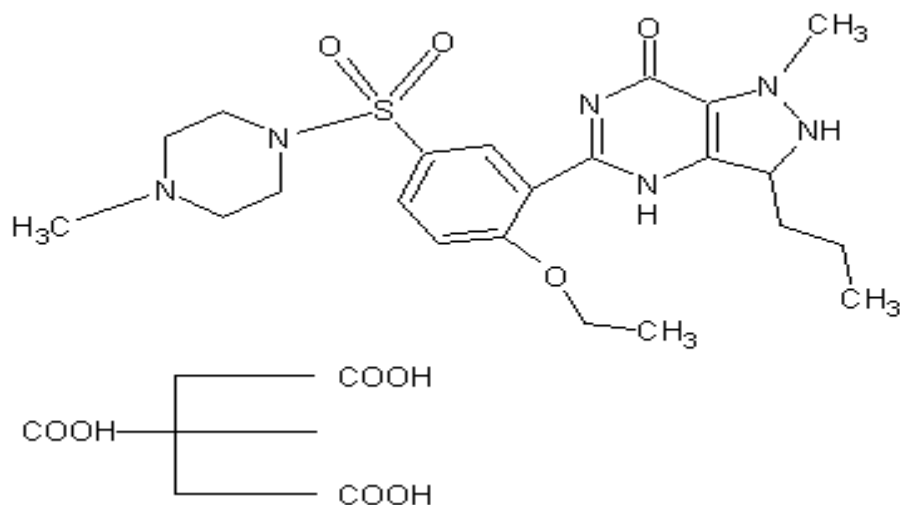


Figure 2.1: Chemical structure of Sildenafil citrate.

Sildenafil is an ordinary ampholyte, typically neutral at physiological pH, as it has 2 pKa values viz, $pK_{a1}=7.10$ (weak acidity due to the amide at the pyrazolopyrimidine ring) and $pK_{a2}=9.84$ (mildly basic due to Ns of piperazine ring) (18). It is relatively lipophilic having a partition coefficient ($\log P$) of 2.7-3.18, and melts within a range of 194-199°C. Sildenafil citrate is relatively stable over a wide range of physical and chemical conditions (16).

2.2 CLINICAL PHARMACOLOGY OF SILDENAFIL CITRATE

2.2.1 Mechanism of action of sildenafil and pathophysiology of PAH

Sildenafil citrate is a selective PDE 5 enzyme inhibitor indicated for the management of PAH (WHO Group 1) in adults and children. It exerts its vasodilatory activity through elevation of cGMP by inhibiting its breakdown by PDE 5, leading to the reduction of symptoms of PAH (19).

Pulmonary arterial hypertension is the first broad group in the WHO classification of pulmonary hypertension. It is further subdivided into primary, genetic, drug or toxin induced, persistent pulmonary hypertension of the newborn (PPHN), and PAH associated with other systemic diseases (1). PAH causes vasomotor imbalance in the pulmonary vascular bed leading to constriction of the blood vessels with their consequent restructuring, inflammation and the ultimate luminal blockade that may cause thrombosis within the vessels. Subsequently, pulmonary arterial pressure increases due to the high vascular resistance. Consequently, right ventricular malfunctioning ensues leading to low cardiac output hence the progressive and debilitating symptoms of PAH (19). Sildenafil decreases the pulmonary vasculature resistance by promoting pulmonary vasodilation (4).

2.2.2 Dosing recommendations

Dosing recommendations for sildenafil in management of PAH in children are as follows (4):

- In children less than 1 year old, an initial starting dose of 0.2 mg/kg given 4 to 8 hourly. Dose is doubled every 24 hours where blood pressure is stable, to a maximum of a total daily dose of 30 mg.

- In children aged 1 year to 18 years, with a body weight below 20 kg, an initial starting dose of 2.5 mg 8 hourly (tid) or 1 mg 6 hourly (qid) is recommended. The dose may be increased to 5 mg tid or 2.5 mg qid, then to a maximum dose of 10 mg tid or 5 mg qid.
- In children aged 1-18 years with a body weight over 20 kg, an initial dose of 5 mg tid or 2.5 mg qid is recommended, with dose increment to 10 mg tid or 5 mg qid, to a maximum dose of 20 mg tid or 10 mg qid.

2.2.3 Drug interactions, contraindications and side-effects

Sildenafil citrate levels are potentiated by CYP3A4 inhibitors such as erythromycin and reduced by CYP3A4 inducers such as Bonsetan. Severe hypotension may result where SC is used together with other hypotensive agents such as the nitrates (19). Sildenafil citrate should therefore never be used together with oral or intravenous nitrates, in combination with potent CYP3A4 inhibitors such as erythromycin and itraconazole, in myocardial infarction, in non-arteritic anterior ischaemic optic neuropathy, in patients with pulmonary hypertension caused by sickle cell anaemia, in patients with known hereditary degenerative retinal disorders and in patients with severe hepatic impairment (4).

Some of the common side effects encountered with the use of SC include: dyspepsia, diarrhea and vomiting, flushing, headaches, dizziness, visual disturbances, raised intra-ocular pressure, cough, pyrexia and erection (4).

2.3 PHARMACOKINETICS OF SILDENAFIL CITRATE

The conventional sildenafil citrate tablets once administered, result in peak plasma concentrations of SC within 30-120 minutes (9). About 90% of sildenafil citrate is absorbed with 40% bioavailability due to first pass metabolism achieving a volume of distribution of 105 litres.

Protein binding is approximately 96% for SC and its major metabolite, N-desmethyl sildenafil (16).

Sildenafil citrate is completely metabolized in the liver to 16 metabolites, mainly by P450 microsomal isozymes 3A4 (major route) and isozymes 2C9 (minor route). The metabolites are largely excreted in faeces (about 80% of the dose which is absorbed) and to a lesser extent in the urine (16).

2.4 ORO-DISPERSIBLE TABLETS

2.4.1 Overview of orodispersible tablets

Oro-dispersible tablets (ODTs) are a major technological breakthrough in the formulation of a dosage form that is highly convenient and has led to a marked improvement in patient compliance (20). ODTs are designed to disintegrate in the mouth without the aid of water and can be administered to patients who have difficulties swallowing (21). In this respect, it is particularly convenient in dosing for paediatric, geriatric and psychiatric patients (22). Some of the merits of this dosage form are (8,10):

- More stable in comparison with liquid formulations.
- Provides rapid drug delivery, rapid onset of action and is capable of by-passing first pass metabolism through pre-gastric absorption thus higher bioavailability.
- Ensures rapid disintegration and dissolution as well as high dose precision.
- Improved safety due to avoidance of the risk of choking.
- Convenient where access to water is not assured.
- Good mouth feel and no chewing is required.

- Utilizes conventional manufacturing equipment and packaging materials and is therefore cost-effective.
- Has opened up novel opportunities in business through product differentiation and the extension of patents.

This dosage form however has few limitations that should be addressed, such as, relatively high hygroscopicity when openly exposed to the environment therefore must be stored in a dry place, fragility due to relatively low mechanical strength, taste-masking must be employed for bitter-tasting drugs since it disintegrates in the mouth, and may require special packaging for proper stabilization, such as double-foil blister pack with peel-able aluminium-lidding (20) (23).

The conventional techniques employed for this dosage form are: direct compression and use of superdisintegrants, mass extrusion, sublimation, moulding compaction, cotton-candy process, spray-drying, lyophilization, and nanonization. Some of the patented technologies include Zydis®, Orasolv®, Durasolv® and Flashtab® (8). Direct compression with addition of superdisintegrants is the most economical as it employs conventional manufacturing equipment (20).

Oro-dispersible tablet formulations of sildenafil citrate have been developed using synthetic superdisintegrants and commercial adult formulations are available. However, dose specific oral dispersible tablets for children are not available commercially.

2.4.2 Superdisintegrants

Superdisintegrants swell up very fast and aid in rapid break-up of the ODT. Unlike the traditional disintegrants, superdisintegrants are usually effective at low concentrations, typically

1-5% w/w of the dosage unit. Superdisintegrants, similar to the conventional disintegrants, exert their activity based on some of the following mechanisms: swelling, porosity and capillary action (wicking), chemical reaction (acid-base reaction), and enzymatic reaction. The widely used synthetic superdisintegrants include Crospovidone, Croscarmellose sodium, and Sodium starch glycolate (24).

Croscarmellose sodium is insoluble in water and it rapidly swells up to 8 times its original volume. It has a swelling index of $65 \pm 1.7\%$ v/v. It is used at a concentration of up to 5% w/w (24). It exerts its superdisintegrant activity by swelling, wicking and strain recovery (25).

Crospovidone is completely insoluble in water. It rapidly disperses and swells in water. It has a swelling index of $58 \pm 1.5\%$ v/v and is used at a range of 2-5% w/w and it acts by swelling and strain recovery (24,25).

Sodium starch glycolate absorbs water quickly and swells up to 6%. Used at a high concentration, it forms a gel coat hence disintegration is lost. It has a swelling index of $52 \pm 1.2\%$ v/v and is typically used at concentrations of 2-8% w/w (11,24).

Some limitations in the use of synthetic superdisintegrants that render natural superdisintegrants a better substitute include (24):

- They are more hygroscopic hence problematic when using moisture sensitive drugs.
- Croscarmellose and sodium starch glycolate are anionic in nature, thus bind with cationic drugs.
- When placed in an acidic medium, croscarmellose sodium and crospovidone significantly lose their liquid uptake rate hence a reduction in their disintegrant activity.

Natural superdisintegrants have mainly been derived from plant gums and mucilages, which are abundant in nature. Mucilages are secondary plant metabolites which have a high concentration of hydroxyl groups, hence have a robust ability to bind water molecules and swell up to 5 times their initial volume (24). Natural excipients have the advantages of being biodegradable, biocompatible, non-toxic, low cost, provide a nutritional supplement, environmental-friendly processing and local availability (12,26).

Several plant mucilages have been tested and proven to have superdisintegrant activity. Kumar R. *et al.* (27) demonstrated that mucilage of fenugreek seeds showed better disintegration than synthetic superdisintegrants in fast dissolving tablets of metformin. Additionally, Kumar M.U and Babu M.K. (28) in formulating oro-dispersible tablets of diclofenac sodium using fenugreek gum as the natural superdisintegrant, demonstrated that it had better disintegrant property than croscarmellose sodium and sodium starch glycolate. A study carried out by Naazia Zafar *et al.* (14) on fast dissolving tablets of sildenafil 25mg using fenugreek seed mucilage, also revealed that formulations containing this natural superdisintegrant had a shorter disintegration time compared to those of synthetic superdisintegrants.

Ghenge *et al.* (29) established that dried *Plantago ovata* mucilage is suitable in formulating ODTs as a superdisintegrant, by preparing ODTs of amlodipine besylate using different concentrations of *Plantago ovata* mucilage. Further, Shirsand S.B *et al.* (30) showed that results obtained from *Plantago ovata* mucilage in formulation of prochlorperazine maleate were comparable and slightly better than those of crospovidone. Rao *et al.* (31) also concluded that there would be improved effectiveness, better bioavailability and better patient compliance by use of *Plantago ovata* mucilage in ODTs of Carbamazepine.

Lovleen *et al.* (32) in formulating FDTs of aceclofenac using *Lepidium sativum* mucilage concluded that the swelling and wicking characteristics of the mucilage contributed to maximum drug release. In yet another study, Halakatti *et al.* (33) evaluated mucilage and treated agar from *Hibiscus rosa sinensis linn.* in the development of mouth disintegrating tablets of famotidine. They observed that these natural superdisintegrants enhanced rapid disintegration and rapid onset of drug action (33).

2.4.3 *Corchorus olitorius* (Jute plant)

Corchorus is a genus having about 40-100 species of flowering plants belonging to the family Malvaceae. It is known by different common names in different contexts with jute referring to its fibre and its leaves known as mallow leaves, which are consumed as an indigenous leafy vegetable (34). It is easily grown and cultivated year round, with excellent disease and pest resistance and gives stable yields, even under difficult climatic conditions (33). It can be harvested three to four weeks after planting. It is a good nutritional source of protein, vitamins A, C and E, beta-carotene and mineral nutrients like calcium and iron (35). Its fibre has both laxative and carminative effects hence good for bowel movements. In Kenya, the leaves are a favourite dish among the Luhya people of Western Kenya and are locally called *mrenda*, which have been observed to be highly mucilaginous (34). When cooked, it has a slimy texture like that observed with okra. The leaves are simple, alternate and lanceolate, with a length of 5-15cm and the margin is finely notched (34).



Figure 2.2: Image of the leaves of *Corchorus olitorius*

In this work, mucilage from *Corchorus olitorius* (jute plant) leaves was extracted, characterized and used in the formulation of an oro-dispersible tablet of Sildenafil citrate, for use in paediatric patients.

2.4.4 Mucilage

Mucilage is a physiological plant product composed of polysaccharide uranides and proteins (36), a type of soluble fibre of viscous nature that forms a slimy mass in water. Mucilage has a high water holding capacity imparted by the high concentration of hydroxyl groups in the polysaccharides (37). This property imparts a high swelling index thus its use as a superdisintegrant. Plant mucilages have pharmaceutical application as binders, disintegrants, emulsifiers and thickeners (38). Therapeutic uses of mucilage have been investigated such as in the management of cancer, diabetes, immunostimulation, wound-healing and as an antioxidant. The demand for natural mucilages is on the rise with new sources being explored to meet this demand (37). No studies exist on the extraction and characterization of mucilage found in the

leaves of *Corchorus olitorius*.

2.4.5 Other excipients selected for tablet formulation

Microcrystalline cellulose functions as a binder due to its good flow and compaction properties. Its strong binding property results from plastic deformation once subjected to pressure. It also offers some disintegration attributable to swelling or capillary action and has a high dilution potential (23). Microcrystalline cellulose exhibits high porosity. Its porous surface provides adsorption sites where fine drug particles in low dose formulation, as explored in this study, are homogeneously distributed (16).

Mannitol is a polyol sugar which is used as filler. Its superiority over other fillers in an orally dispersible tablet is based on its non-hygroscopic nature, a negative heat of solution which offers a cooling sensation and sweet flavor giving a good mouth feel (23). Powder blends of mannitol as filler have exhibited better flow than fructose blends (16).

Magnesium stearate is a commonly used lubricant, typically used at low concentrations 0.25% to 1% w/w. It should be blended for a short time since protracted blending times lead to increased tablet friability (39).

Colloidal silicon dioxide is a glidant that also has tablet disintegrant property. Its small particle size and large specific surface area impart improved powder flow (39).

Sodium saccharin and strawberry act as sweetening and flavouring agents respectively, incorporated in the formulation for taste masking, since sildenafil citrate has a bitter taste (9).

CHAPTER 3: EXPERIMENTAL

3.1 STUDY DESIGN

This was a comparative laboratory-based experimental study.

3.2 STUDY LOCATION

The study was conducted in the practical laboratory located in the Department of Pharmaceutics and Pharmacy Practice, at the University of Nairobi, Kenya.

3.3 MATERIALS

The plant material 'mrenda' was collected from Western Kenya, Kakamega rainforest area. Sildenafil citrate, mannitol, crospovidone (CPV), colloidal silicon dioxide (CSD), magnesium stearate, sodium saccharin and strawberry flavor were obtained as a donation from Lab and Allied Pharmaceuticals, Nairobi. Sodium starch glycolate (SSG) and croscarmellose sodium (CMS) were provided by the School of Pharmacy of The University of Nairobi. All the materials were of pharmaceutical grade.

3.4 EQUIPMENT/APPARATUS

The following equipment were used for the experimental study: water bath, oven (Mettler, Germany) dessicator, pH meter, Cole-Parmer® rotational viscometer , phase Contrast Microscope(Nikon, Japan), Fourier Transform Infrared spectrophotometer (Shimadzu, Tokyo, Japan), ultra-violet spectrophotometer (Shimadzu, Tokyo, Japan) analytical weighing balance (Sartorius, England), rotary single punch compression machine (Inweka, India), electronic

hardness tester (Schleuniger & Co., Germany), friability tester (Erweka, Germany) and digital vernier calipers.

3.5 EXTRACTION

The extraction method was modified from P. Nazni and P. Vigneshwar (40) The leaves of *Corchorus olitorius* were washed with water to remove any foreign material, dried at 50° C for 24 hrs and their size reduced using a cutter mill. The milled material, 400 gms, was soaked in distilled water for 6 h at 60°C with continuous stirring using a magnetic stirrer, until the mucilage was completely released into the water. The solid material was then filtered off using a modified muslin cloth. Mucilage was then flocculated from the filtrate by pre-extraction with 96% ethanol for duration of 24 hrs at room temperature. The mucilage was recovered by washing with 3 volumes of acetone, followed by drying in an oven at 45°C. The dried mucilage was then ground using mortar a pestle and the resultant powder sieved using sieve number 70, weighed and stored in a dessicator until use. The process of filtration and the dried mucilage powder are illustrated in Figures 3.1 and 3.2.



Figure 3.1: Filtration using a modified muslin cloth



Figure 3.2: Dried *Corchorus olitorius* leaves mucilage powder

3.6 PHYSICOCHEMICAL CHARACTERISATION OF THE ISOLATED MUCILAGE POWDER

3.6.1 Organoleptic characterisation of the isolated mucilage powder

The extracted mucilage was evaluated for the organoleptic properties of taste, odour, colour and texture.

3.6.2 Identification

Iodine test: 100 mgs of dried mucilage powder was taken and 1ml of 0.2 N solution of iodine added. No color observed in solution would confirm the absence of starch hence identity as mucilage, which is a non-starch polysaccharide.

3.6.3 Swelling index

One gram of the *Corchorus olitorius* mucilage powder was placed in a 50 ml measuring cylinder. 25 ml of distilled water was added and the mixture shaken thoroughly every 10 min for 1 h. It was then left to stand for 24 hrs and volume occupied by the mucilage powder noted. The swelling index (SI) was calculated using formula:

$$\text{Swelling index} = \frac{\text{final volume} - \text{initial volume}}{\text{final volume}} \times 100$$

3.6.4 Loss on drying

One gram of *Corchorus olitorius* mucilage powder was accurately weighed and dried in a hot air oven at 105°C with the weight being checked at intervals of 10 min. When there was no further change in the weight of powder, the loss on drying was calculated using the equation:

$$\text{Loss on drying} = \frac{\text{Initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

3.6.5 pH of mucilage

The pH of a 1% w/v aqueous solution of the *Corchorus olitorius* mucilage powder was determined using a digital pH meter.

3.6.6 Viscosity

1% w/v of the mucilage in water was prepared by dilution in warm water, and the viscosity determined using a Cole- Parmer[®] rotational viscometer, spindle L₂ and torque 50.8%.

3.6.7 Solubility of mucilage

The solubility was determined by shaking the powdered mucilage in different solvents viz warm water, cold water, acetone, ethyl alcohol and chloroform.

3.7 MICROMERITIC PROPERTIES OF THE ISOLATED MUCILAGE POWDER

3.7.1 Particle size and shape determination

Mucilage size and shape was determined by optical microscopy, using a Nikon®, phase contrast microscope.

3.7.2 Angle of repose

The *Corchorus olitorius* mucilage powder was poured through a funnel, which was then vertically raised to a maximum cone height. Radius of the heap was determined and the angle of repose (θ) calculated thus:

$$\text{Tan } \theta = \frac{h}{r}$$

Where: θ = Angle of repose; h = Height of pile; r = Radius of pile

3.7.3 Bulk density

This is the mass of the powder divided by the bulk volume. It was determined by pouring the mucilage powder into a graduated measuring cylinder and the bulk volume and the actual weight of the powder determined. The bulk density was then calculated using the formula:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume}}$$

3.7.4 Tapped density

Tapped density was determined by tapping the graduated cylinder with a weighed mass of powder 100 times. The final volume occupied by the powder was noted and the tap density calculated using the formula:

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped density}}$$

3.7.5 Hausner's ratio

Hausner's ratio gives an indication of the ease of powder flow. It was calculated using the formula (14):

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

3.7.6 Compressibility Index

Compressibility index gives a measure of free flow of powder and an indication of the ease with which a material can be induced to flow, and is calculated thus (14):

$$\text{Compressibility index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Table 3.1 Formula for Preparation of Sildenafil Citrate Oral Dispersible Tablets in mgs

Batch	SC	Mannitol	Mucilage	CMS	CPV	SSG	MCC	CSD	Mg Stearate	Sodium Saccharin	Strawberry flavor	Total Weight
SC01	2.5	73.5	5.0	-	-	-	37.5	1.5	1.5	2.5	1.0	125
SC02	2.5	71.0	7.5	-	-	-	37.5	1.5	1.5	2.5	1.0	125
SC03	2.5	68.5	10	-	-	-	37.5	1.5	1.5	2.5	1.0	125
SC04	2.5	73.5	-	5.0	-	-	37.5	1.5	1.5	2.5	1.0	125
SC05	2.5	71.0	-	7.5	-	-	37.5	1.5	1.5	2.5	1.0	125
SC06	2.5	68.5	-	10	-	-	37.5	1.5	1.5	2.5	1.0	125
SC07	2.5	73.5	-	-	5.0	-	37.5	1.5	1.5	2.5	1.0	125
SC08	2.5	71.0	-	-	7.5	-	37.5	1.5	1.5	2.5	1.0	125
SC09	2.5	68.5	-	-	10	-	37.5	1.5	1.5	2.5	1.0	125
SC10	2.5	73.5	-	-	-	5.0	37.5	1.5	1.5	2.5	1.0	125
SC11	2.5	71.0	-	-	-	7.5	37.5	1.5	1.5	2.5	1.0	125
SC12	2.5	68.5	-	-	-	10	37.5	1.5	1.5	2.5	1.0	125

3.10 EVALUATION OF THE TABLETS

The formulated sildenafil citrate ODTs were evaluated for weight variation, hardness, thickness, friability, wetting time, water absorption ratio, in-vitro dispersion time, content and content uniformity as per the USP 29 guidelines.

3.10.1 Weight Variation

Twenty tablets were selected randomly, weighed and the average weight noted. The individual tablet was then weighed and percentage difference from the average weight calculated.

3.10.2 Hardness

Ten tablets were randomly selected from every batch and hardness tested using the electronic tablet hardness tester.

3.10.3 Thickness

Thickness was measured using electronic digital vernier calipers. Ten tablets were selected from each batch and their mean thickness and standard deviation determined.

3.10.4 Friability

Friability was evaluated using the Erweka® Friabilator. Twenty tablets were randomly selected and placed in the friabilator for 100 revolutions. Tablets were dusted clean and the final weight noted. Friability was calculated by the formula:

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

3.10.5 Phosphate buffer preparation

Phosphate buffer solution of pH 6.8 was prepared by accurately weighing 0.68 gms of potassium dihydrogen orthophosphate into a 100 ml volumetric flask. Distilled water was then added and the flask sonicated for 5 minutes to completely dissolve the solute. The solution was then made to mark with distilled water. The pH was finally adjusted using sodium hydroxide, to 6.8 (16).

3.10.6 Wetting time

Into a petri-dish containing 5 stacked pieces of tissue paper, 10 ml of phosphate buffer pH 6.8 at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ containing eosin (a water soluble dye) was poured. One tablet was placed gently on the stacked tissue papers and time taken for the solution to succeed onto the surface of the tablet noted as the wetting time.

3.10.7 Water absorption ratio

A piece of tissue paper was folded twice and placed in a petridish containing 6 ml of phosphate buffer solution. A pre-weighed tablet was placed on the paper and time taken for its complete wetting noted. The wetted tablet was then weighed. Water absorption ratios were calculated using the equation below.

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where, R=Water absorption ratio; W_a =Weight of the tablet after absorption; W_b =Weight of the tablet before absorption

3.10.8 *In-vitro* dispersion time

In-vitro dispersion time is used as an indicator of disintegration time. Phosphate buffer solution pH 6.8 (10 ml) at $37^{\circ}\text{C}\pm 0.5^{\circ}\text{C}$ was poured into a petri-dish. One tablet was placed at the center of the petridish and the time taken for the tablet to disperse completely into very tiny particles noted as the *in-vitro* dispersion time.

3. 10.9 Preparation of standard graph of sildenafil citrate

Ten milligrams of SC standard (potency 99.4%) were accurately weighed into 100 ml volumetric flask (VF), dissolved and made to the mark using 0.01N HCl, to obtain a standard stock solution of 100 $\mu\text{g}/\text{ml}$. Working standards of SC,(4,5,8,10,12,15,20,25,30,35 ml) were transferred in a series of 100 mls VFs and diluted to mark with 0.01N HCl to obtain (4,5,8,10,12,18,20,25,30,35 $\mu\text{g}/\text{ml}$) standard solutions respectively. To obtain the wavelength of maximum absorption (γ_{max}) 10 $\mu\text{g}/\text{ml}$ standard solution was selected and scanned in the UV spectrophotometer in the 200-300nm range. A selective γ_{max} was observed at 292 nm. Absorbance values OF the prepared standard concentrations were recorded at the wavelength (γ_{max}) of 292nm as shown in Table 3.2. From this data, a standard curve of SC was plotted as illustrated in Figure 3.3:

Table 3.2: Standard Concentrations and Corresponding Absorbance values

Concentration of Standard ($\mu\text{g/ml}$)	Absorbance (nm)
0	0
3	0.068
4	0.084
5	0.102
8	0.176
10	0.216
12	0.252
18	0.416
20	0.548
25	0.548
30	0.654
35	0.768

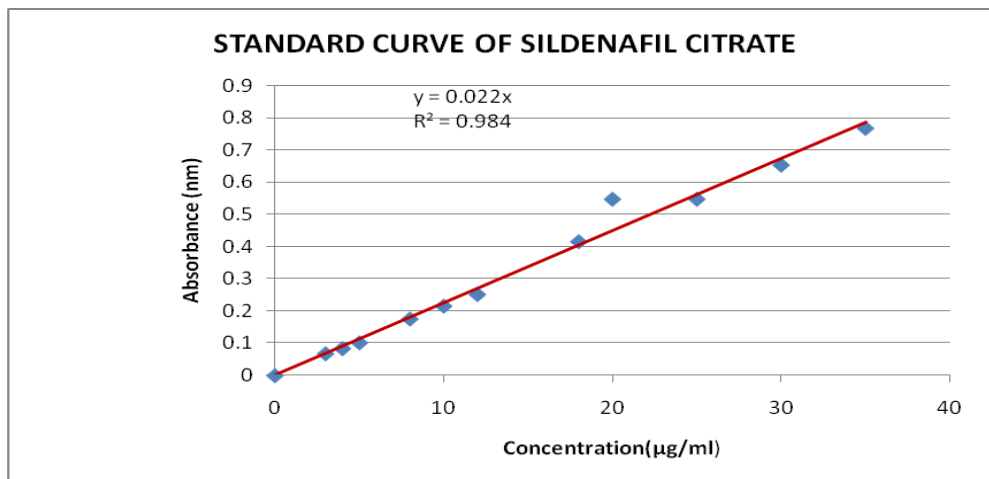


Figure. 3.3: Standard Curve of the API Sildenafil Citrate.

3.10.10 Assay and content uniformity

Ten SC tablets from each batch were crushed using mortar and pestle and the powder weighed. An amount equivalent to 2.5 mg of Sildenafil citrate was transferred into 100 ml VF containing 0.01N HCl. The flask was sonicated and the solution made to volume with 0.01N HCl and filtered using Whatman® filter paper. A 20 ml aliquot was taken in a 50 ml VF and made to volume with 0.01N HCl to obtain 10 µg/ml of SC. The API content was analyzed using the UV spectrophotometer at a wavelength of 292 nm and calculated using the standard graph of sildenafil citrate. For content uniformity, 30 tablets were randomly selected from each batch and 10 of the tablets individually assayed (41).

3.10.11 Analysis of data using single factor ANOVA

For comparison of the formulations, a single factor Analysis of Variance test (using Microsoft Excel®) at 5% significance level was done for the Dispersion time, wetting time and water absorption ratio of the *Corchorus olitorius* mucilage formulations, and those containing the synthetic superdisintegrants.

CHAPTER FOUR: RESULTS AND DISCUSSION

4.1 PHYSICOCHEMICAL CHARACTERISTICS OF ISOLATED MUCILAGE

Powdered mucilage of *Corchorus olitorius* was successfully extracted at a yield of 7% w/w. This amount was quite significant, given the anticipated small quantity needed per tablet, in its role as a superdisintegrant.

The physicochemical properties of the extracted *Corchorus olitorius* mucilage are outlined in Table 4.1. Organoleptic characterization showed that *Corchorus olitorius* mucilage is a powder, ash brown in colour, has a mucilaginous (mucourish) taste, a fine texture and characteristic smell.

There was no observed colour change in the iodine test, hence absence of starch. Mucilage is a non-starch heterogeneous branched polysaccharide formed from galactose, glucose, arabinose, and rhamnose joined to uronic acid residues by glycosidic linkages (42). Mucilage therefore contains several hydroxyl groups that impart the high swelling index as seen at 85.7% in the current study. The loss on drying of 0.71%, is within the acceptable range for suitability in tablet formulation of below 1%.

The pH of 1% w/v solution of the mucilage was 6.605, which is non-irritating to mucous membranes (36). The viscosity of 35.1 centipoises indicates moderate ease of flow in solution. The mucilage forms a dilute suspension of low viscosity that has no impact on drug release. The isolated mucilage was slightly soluble in cold water, soluble in warm water, acetone and ethyl alcohol and completely insoluble in non-polar solvent, chloroform, hence it is quite polar.

Table 4.1: Physicochemical Characterisation of *Corchorus olitorius* mucilage

PARAMETER	RESULT
State	Powder
Colour	Brown
Odour	Characteristic
Taste	Mucilaginous
Texture	Very fine
Iodine test	No colour change. Absence of starch.
Swelling Index	85.7%
Loss on drying	0.71%
pH (1% w/v)	6.605
Viscosity	35.1 cP
Solubility	Slightly soluble in cold water and acetone, soluble in warm water, insoluble in ethyl alcohol and chloroform.
Particle size	1-4 μm
Particle shape	Sub-spherical and irregular
Bulk density	0.3362 g/cm^3
Tapped density	0.4305 g/cm^3
Hausner's Ratio	1.28
Compressibility index	21.9%
Angle of repose	36.4°

Micromeritic tests revealed that the mucilage powder is suitable for use in formulation of a solid oral dose, with small particle size range of 1-4 μm on the optical grid of the light microscope and sub-spherical or irregular shapes as illustrated in Figure 4.1.

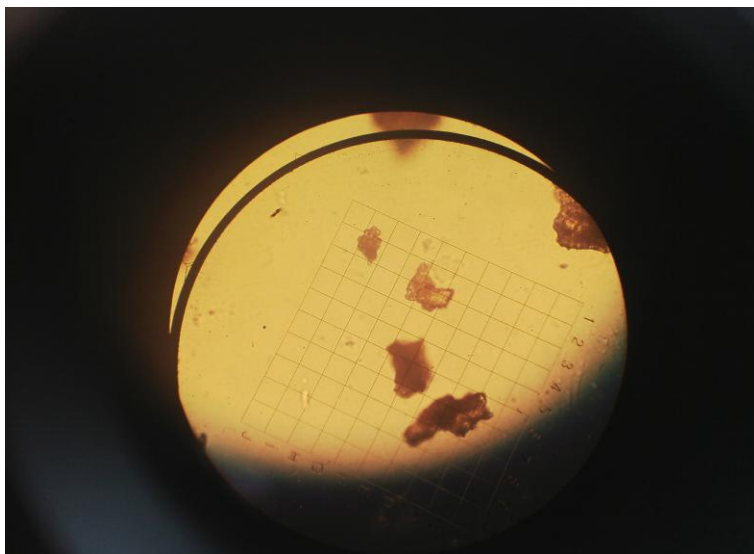


Figure 4.1: Microscopic view of *Corchorus olitorius* mucilage at $\times 500$ i.e (eye-piece lens $\times 10$ and objective lens $\times 50$)

The particles were light brown in colour, singly distributed and having a puffy appearance. Mucilage powder had an angle of repose of 36.4° indicating fair flow properties; Hausner's ratio and compressibility index of 1.28 and 21.9% respectively, a passable flow character according to USP 29.

4.2 PRELIMINARY FORMULATION STUDIES

4.2.1 Drug excipient compatibility studies using Infra-red spectroscopy

Individual components and binary mixtures of the API Sildenafil citrate and all other excipients and those of mucilage and all other ingredients were prepared, and their interactions checked using a Shimadzu[®] Fourier Transform infra-red spectrophotometer. The infra-red spectra were obtained in the range of $4000-600\text{ cm}^{-1}$. The spectra of SC alone, mucilage alone and binary mixture of SC and superdisintegrants are as illustrated in figures 4.2-4.7 and appendices.

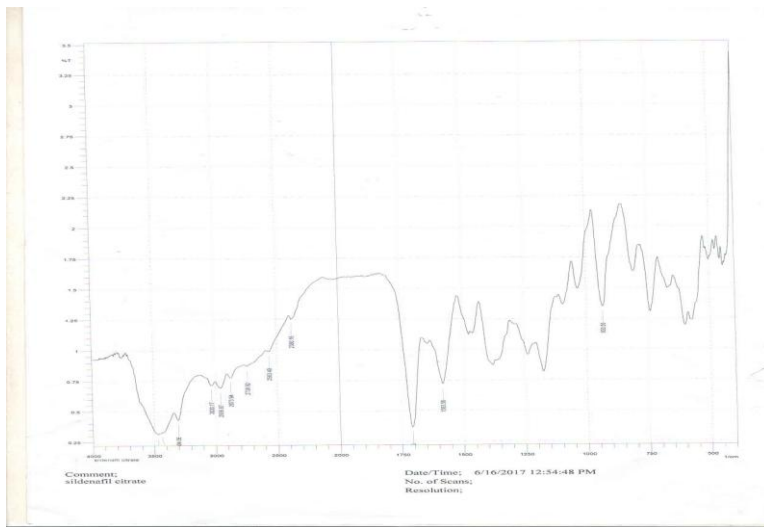


Figure 4.2: IR spectrum of Sildenafil citrate

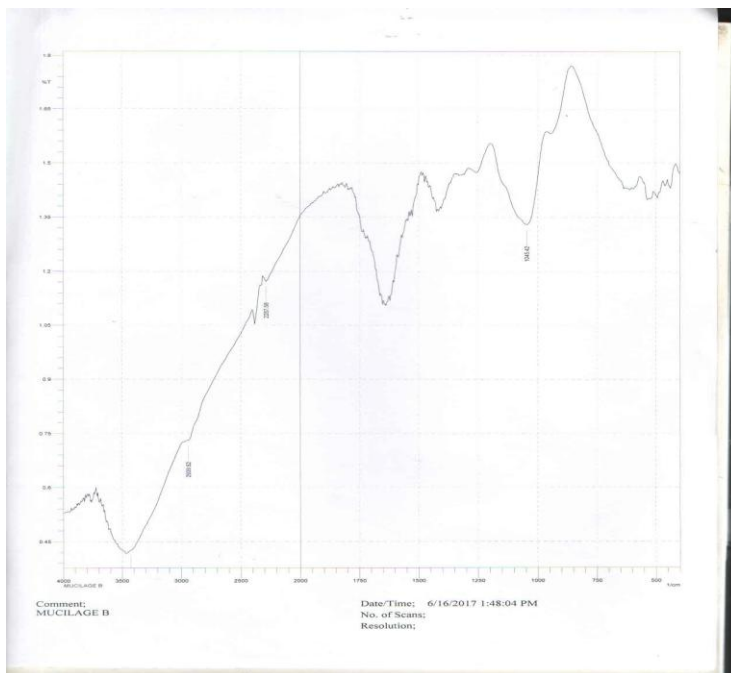


Figure 4.3: IR spectrum of *Corchorus olitorius* mucilage

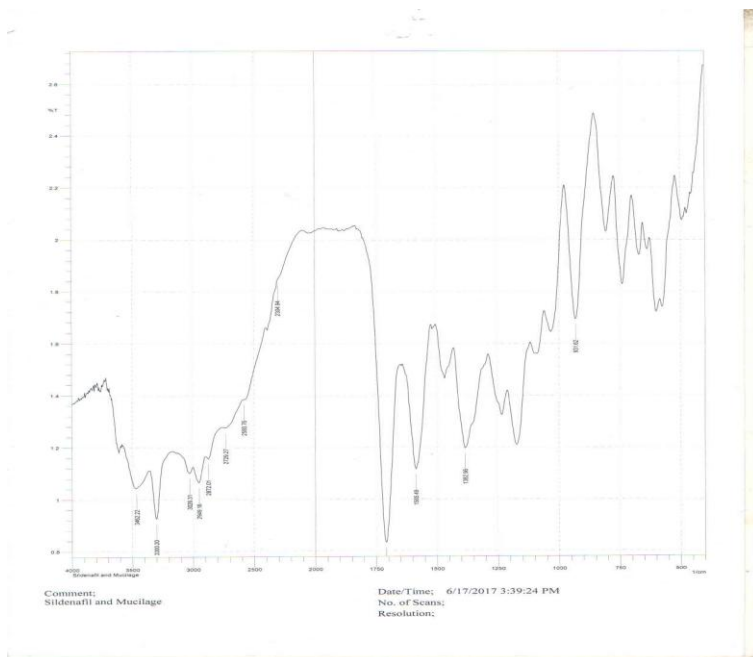


Figure 4.4: IR Spectrum of Binary blend of Sildenafil citrate and *Corchorus olitorius* mucilage

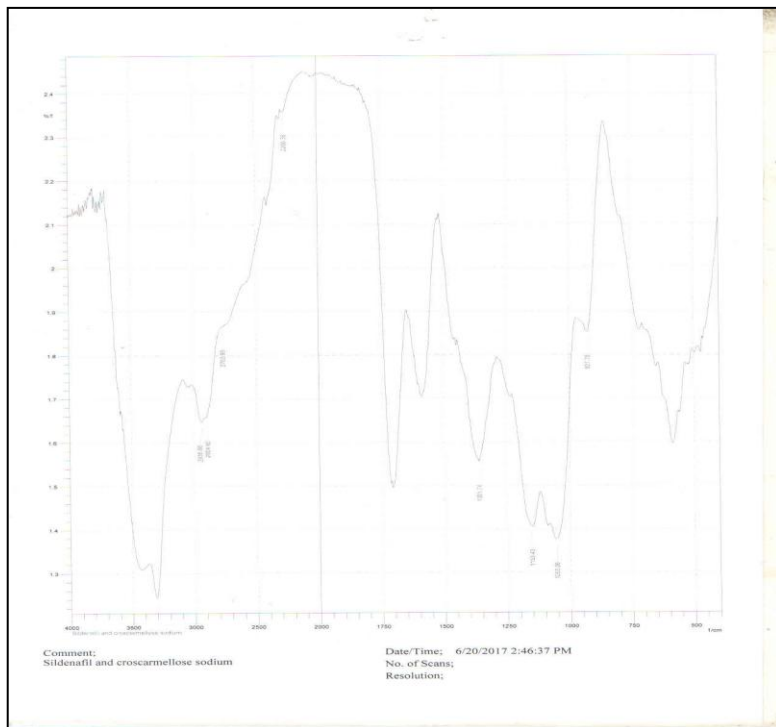


Figure 4.5: IR Spectrum of Binary blend of Sildenafil citrate and Crosscarmellose sodium

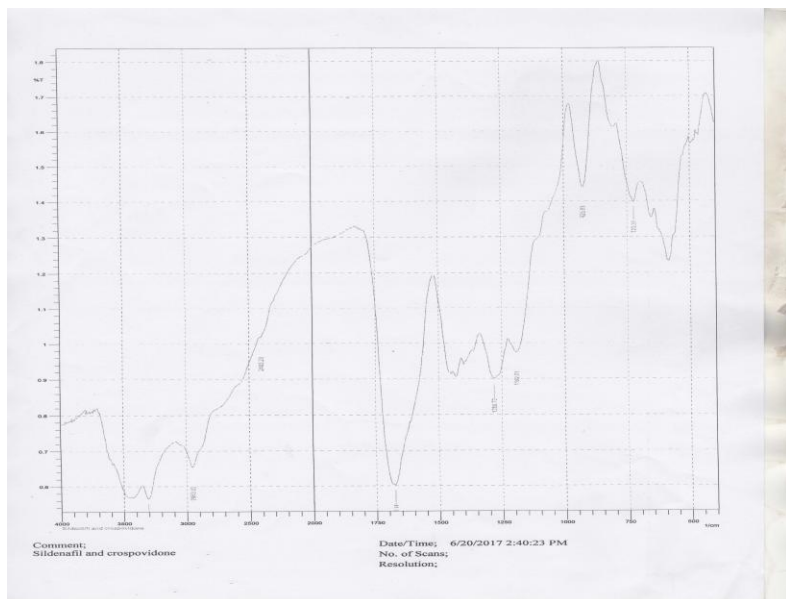


Figure 4.6: IR Spectrum of Binary blend of Sildenafil citrate and Crospovidone

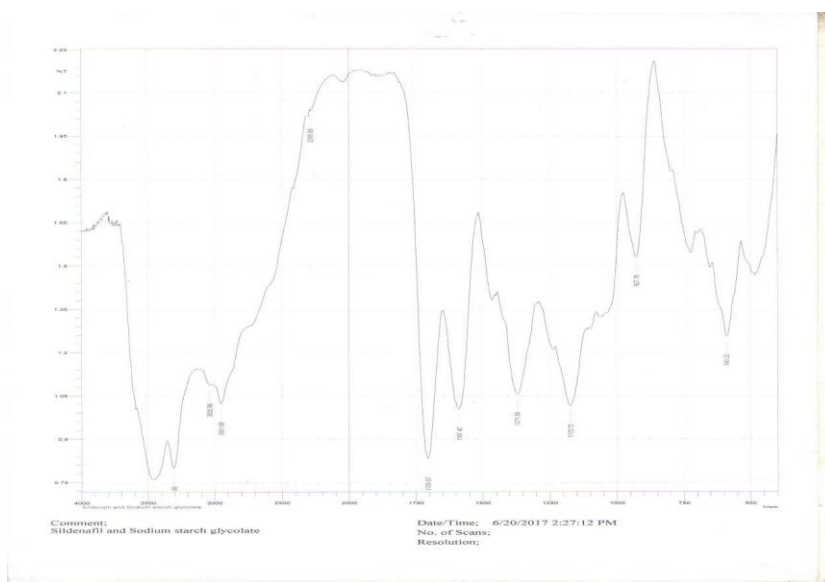


Figure 4.7: IR Spectrum of Binary blend of Sildenafil citrate and Sodium starch glycolate

There were no chemical group interactions from examination of the spectra. This predicts absence of drug excipient interactions which would be as a result of bond formation between drug and the excipients (43).

4.2.2 Micromeritic tests on powder blends

The flow properties of the prepared powder blends (see Table 3.1) are presented in Table 4.2.

According to the USP 29, Compressibility index is an indirect measure of the bulk density, size and shape, moisture content, surface area and the cohesiveness of materials. Although it is based on the method used, it gives an indication of the powder blend ability to flow. It is directly proportional to the Hausner's ratio. The USP 29 scale of flowability is given in Appendix 10. The powder blends used in formulation of all the batches exhibited fair to passable flow character, hence suitable for tablet formulation.

Table 4.2: Micromeritic studies of the powder blends

Batch Number	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Hausner's Ratio	Compressibility Index (%)	Angle of Repose (°)
SC01	0.5208	0.6944	1.33	25.0	41.0
SC02	0.5682	0.7353	1.29	22.7	41.4
SC03	0.5435	0.6944	1.28	21.7	40.0
SC04	0.5435	0.6944	1.28	21.7	41.4
SC05	0.5208	0.6578	1.25	20.8	43.6
SC06	0.5208	0.6578	1.25	20.8	41.4
SC07	0.5208	0.6944	1.33	25.0	42.7
SC08	0.5435	0.6944	1.28	21.7	41.0
SC09	0.5208	0.6944	1.33	25.0	42.7
SC10	0.5208	0.6944	1.33	25.0	42.7
SC11	0.5208	0.6944	1.33	25.0	40.6
SC12	0.5208	0.6579	1.26	20.8	40.0

The angle of repose, also dependent on method used in its determination, is related to the inter-particulate resistance to movement. The angle of repose should not exceed 50° for the powder to

be acceptable for manufacture. Carr's classification of flow property and corresponding angle of repose is given in Appendix 11. The powder blends in this study had values of angle of repose of between 40° and 44°, exhibiting fair and passable flow properties and therefore acceptable for tablet manufacture.

4.3: PHARMACOPOEIAL EVALUATION OF FORMULATED TABLETS

4.3.1: Tablet Formulation

Twelve batches of Sildenafil citrate tablets containing increasing concentrations of the synthetic superdisintegrants and *Corchorus olitorius* mucilage were formulated by direct compression using a rotary single punch compression machine. The *Corchorus olitorius* mucilage containing tablets are depicted in Figure 4.8. They were subjected to pharmacopoeial tests as outlined in Table 4.3.



Figure 4.8 Sildenafil tablets containing 5 mg, 7.5 mg and 10 mgs of *Corchorus olitorius* mucilage respectively.

TABLE 4.3: Pharmacopeial parameters of the formulated sildenafil citrate oro-dispersible tablets

BATCH	WEIGHT (mg)	HARDNE- SS (N)	THICKNE- SS (mm)	FRIABI- LITY	WETTING TIME (s)	WATER ABSORPTI- ON RATIO	DISPERSION TIME (s)	ASSAY (%)	CONTENT UNIFORMITY (%)
SC01	132±4.62	23.80±3.25	1.3±0.06	4.47	5.67±0.58	4.91±1.79	20.67±1.15	82.4±8.79	100±0.10
SC02	129±4.20	15.33±9.61	1.3±0.06	6.30	5.60±1.15	7.61±2.60	19.33±1.15	92.9±5.92	100±0.05
SC03	129±4.68	9.67±2.34	1.2±0.00	10.89	5.33±0.58	5.42±1.42	18.67±1.15	92.0±5.11	100±0.11
SC04	132±6.06	32.00±2.28	1.3±0.06	1.79	5.33±0.58	2.17±0.89	19.33±1.15	92.9±2.60	100±0.10
SC05	136±8.03	30.30±7.53	1.2±0.00	2.16	13.67±0.58	4.84±1.59	25.67±0.58	101.1±6.52	100±0.05
SC06	134±5.49	24.40±4.92	1.2±0.06	8.29	13.00±2.00	2.78±0.29	24.33±0.58	90.9±1.21	100±0.08
SC07	133±3.79	30.20±7.00	1.2±0.00	1.52	2.00±0.00	2.86±2.29	4.33±0.58	85.8±3.35	100±0.05
SC08	133±4.27	30.00±7.35	1.2±0.00	1.71	2.00±0.00	1.80±0.95	6.33±2.08	94.1±2.86	100±0.12
SC09	129±3.07	31.00±7.98	1.2±0.00	1.40	2.00±0.00	1.01±0.27	4.00±0.00	98.3±12.44	100±0.03
SC10	133±6.23	13.00±6.16	1.3±0.06	7.60	15.67±2.52	3.22±0.48	20.00±1.00	93.3±2.50	100±0.05
SC11	130±5.46	15.6±5.18	1.1±0.06	4.96	15.00±3.00	4.39±2.42	17.00±1.00	106±2.59	100±0.05
SC12	135±8.37	16.4±6.23	1.3±0.06	2.95	15.30±2.00	1.42±0.23	17.67±1.15	101±3.15	100±0.07

4.3.2: Weight variation

Twenty tablets, selected randomly were assessed for uniformity of weight which was reported as mean weight \pm standard deviation in Table 4.5. All batches passed the weight uniformity test, whereby not more than two tablets intra-batch varied by ± 7.5 % deviation, according to official specifications.

4.3.3: Assay for content:

The results revealed that all batches except SC 01 and SC 07 were within the compendial limits of 90%-110% drug content for low dose formulations according to the USP 29. The slightly low API content in the two batches could have resulted from undiscernable factors such as incomplete or non-homogenous mixing of the API with the other excipients.

4.3.4: Content uniformity

Weight variation on its own does not guarantee uniformity of content per tablet, and is therefore necessary to assay each tablet individually to establish that the API is uniformly distributed across the units. A content uniformity test was therefore done by assaying 10 tablets randomly selected from 30 tablets of each batch. All the batches conformed to the specifications, where the RSD should be less than 6% and the values be within 85-115% of the stated content (41).

4.3.5: Hardness, thickness and friability

These parameters are usually dependent on the compression pressure which had to be varied in-process so as to attain a hardness of 10-35N, ideal for dispersible tablets. This had to be done manually, given the make of the compression machine, precluding standardization in cases where automatic controls are used. The achieved hardness and thickness could not guarantee

robust tablets which failed the friability test. This is a common challenge with oro-dispersible tablets which are usually fragile due to the low mechanical strengths involved and the hygroscopic nature of superdisintegrants.

4.3.6: Wetting time, water absorption ratio and in-vitro dispersion time

These tests were conducted in phosphate buffer at a pH of 6.8 and temperature of $37\pm 0.5^{\circ}\text{C}$ so as to simulate the conditions of saliva. There was a direct relationship between the wetting time and water absorption ratio to the in-vitro dispersion time for all the batches. The dispersion time was used as a modified disintegration test due to the very short disintegration times involved. The end point for complete disintegration is the state whereby any residue that remains is a soft mass, without a palpable firm core. The in-vitro dispersion test for the mucilage containing tablets is illustrated in Figure 4.9.

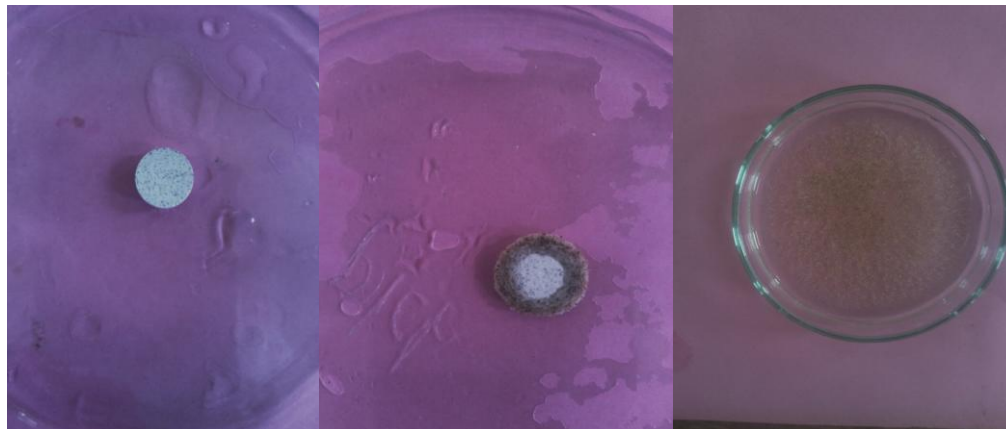


Figure 4.9: *In-vitro* dispersion test for the oro-dispersible tablets of Sildenafil citrate containing *Corchorus olitorius* mucilage, before, during and after complete dispersion

All the batches met the FDA specification for oro-dispersible tablets, of disintegration time of less than 30 seconds. The mean dispersion times for batches containing *Corchorus olitorius* mucilage powder at 5 mg, 7.5 mg and 10 mg were 20.67, 19.33 and 18.67 seconds respectively.

The dispersion time was observed to decrease with increasing mucilage concentrations. Disintegration of the mucilage containing tablets is similar to the sodium starch glycolate containing tablets, which is achieved by swelling from the edges, which is very rapid initially, but rather slow at the end due to formation of gel coat that slows water movement to the remaining tablet core.

The dispersion time of the SC tablets containing *Corchorus olitorius* mucilage compared closely with that of SC tablets containing sodium starch glycolate and those containing croscarmellose sodium. However, there was a significant difference for the SC tablets containing mucilage with those containing crospovidone in the wetting and *in-vitro* dispersion times. The water absorption ratios were not significantly different across the batches. This was confirmed using single factor Analysis of Variance at 5% significance level on Microsoft® Excel as shown in Table 4.4:

Table 4.4: Comparison of wetting time, water absorption ratio and dispersion times of Sildenafil citrate oro-dispersible tablets using single factor ANOVA test

PARAMETER	SCMU vs. SCCS	SCMU vs. SCR V	SCMU vs. SCSG
Wetting Time	P=0.0021 Fcal>> FCritical	P=0.0015 Fcal>>Critical	P=0.00043 Fcal>>> FCritical
Water Absorption Ratio	P=0.213 Fcal<Fcritical	P=0.048 Fcal> FCritical	P=0.18 Fcal< F Critical
Dispersion Time	P=0.015 Fcal> FCritical	P=0.00062 Fcal>>> FCritical	P=0.071 Fcal< FCritical

KEY: SCMU, SCCS, SCR V and SCSG: Sildenafil Citrate tablets containing *Corchorus olitorius* mucilage, croscarmellose sodium, crospovidone and sodium starch glycolate respectively.

4.4: CONCLUSION AND RECOMMENDATIONS

In this work, mucilage powder of *Corchorus olitorius* leaves was successfully extracted and characterized for its physicochemical characteristics. It is evident from the results that *Corchorus olitorius* mucilage powder is suitable for tablet manufacture with potential for use as a superdisintegrant owing to its high swelling index of 85.7%.

Following the DECS analysis by IR on the API sildenafil citrate and all excipients, no predictable drug-excipient interactions were observed. Powder flow characterization on all powder blends suggested passable flow character and direct compression was used to formulate the sildenafil citrate tablets. Each of the four superdisintegrants, *Corchorus olitorius* mucilage powder, croscarmellose, crospovidone and sodium starch glycolate was incorporated at 5 mg, 7.5 mg and 10 mg to make a total of twelve batches of 2.5 mg sildenafil citrate tablets.

Sildenafil citrate (2.5 mg) oro-dispersible tablets were successfully formulated and pharmacopoeial evaluation demonstrated that they are a suitable dosage form for paediatrics, with good distribution of the API and low in-vitro dispersion times of less than 30 seconds. The *in-vitro* dispersion time of sildenafil citrate ODTs containing *Corchorus olitorius* mucilage compared closely with that of tablets containing croscarmellose sodium as well as those containing sodium starch glycolate. The in-vitro dispersion time was observed to decrease with increasing concentrations of the superdisintegrant. *Corchorus olitorius* mucilage has the advantage of being non-toxic, a nutritional supplement and eco-friendly, therefore, higher concentrations can be safely used to achieve even lower *in-vitro* dispersion times.

Further work should be carried out to establish the optimum concentration of *Corchorus olitorius* mucilage powder for its superdisintegrant activity.

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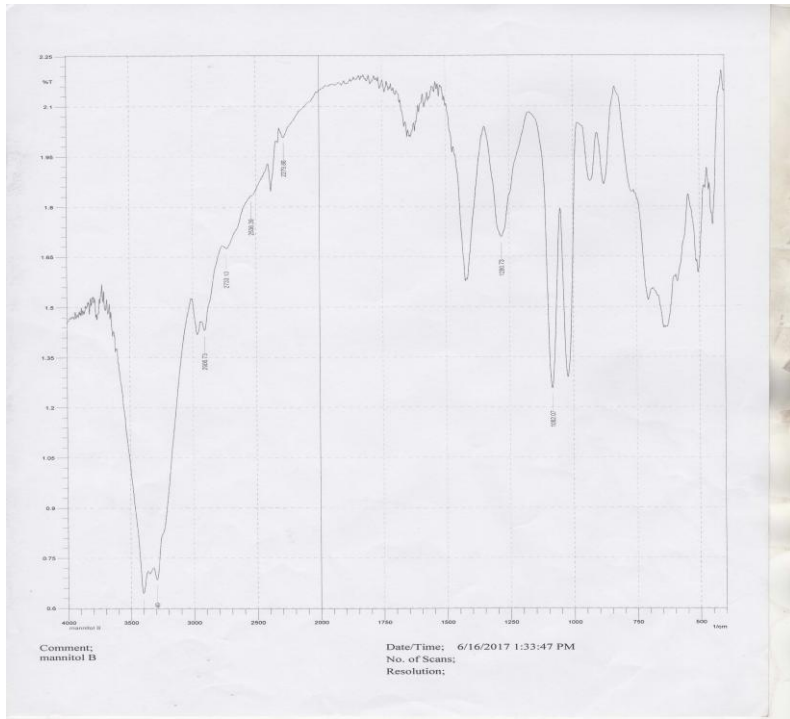
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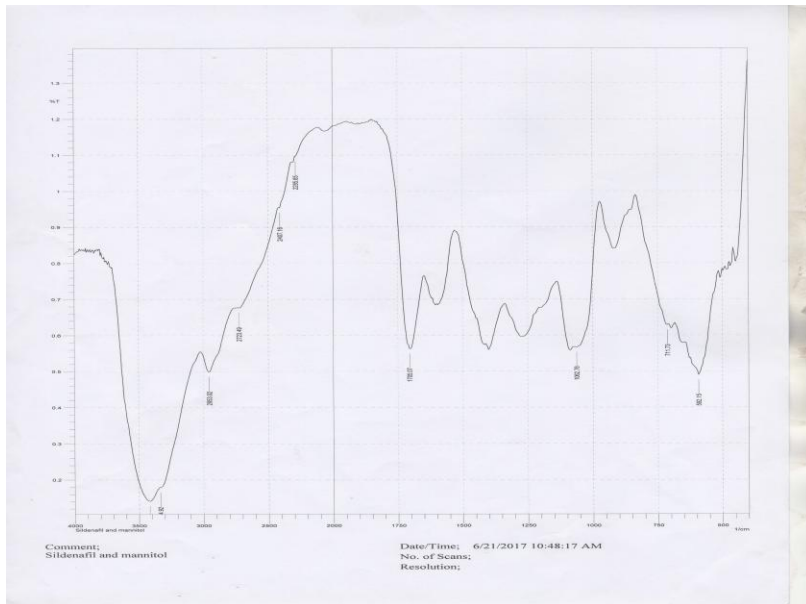
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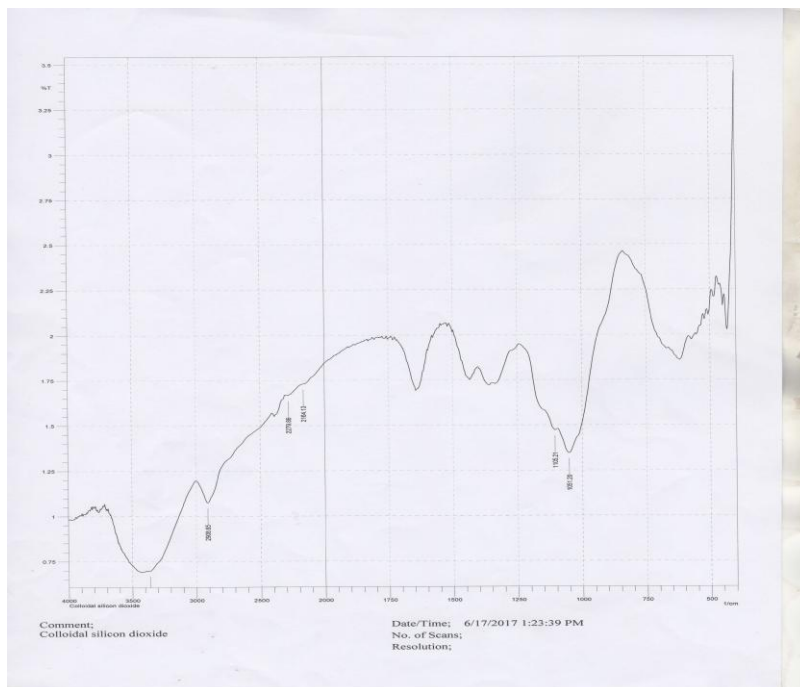
APPENDICES



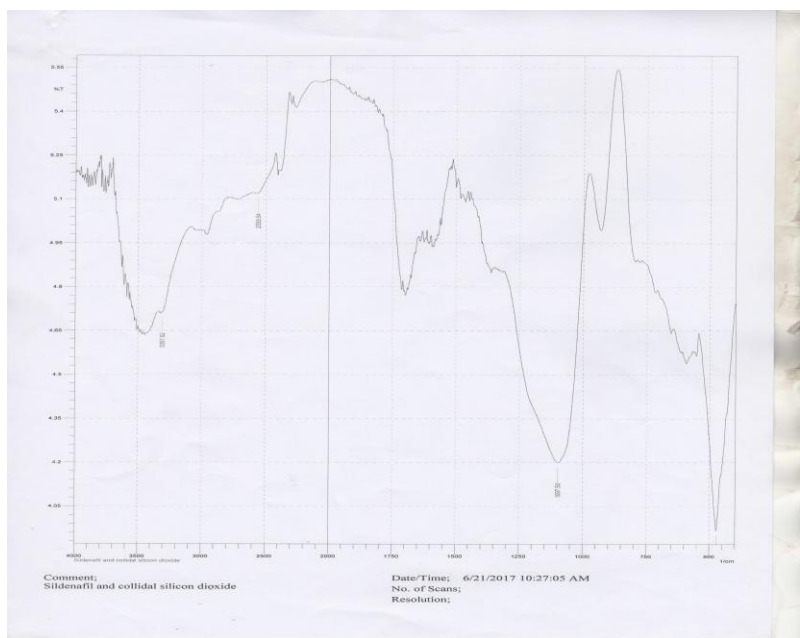
Appendix 1: IR Spectrum of Mannitol



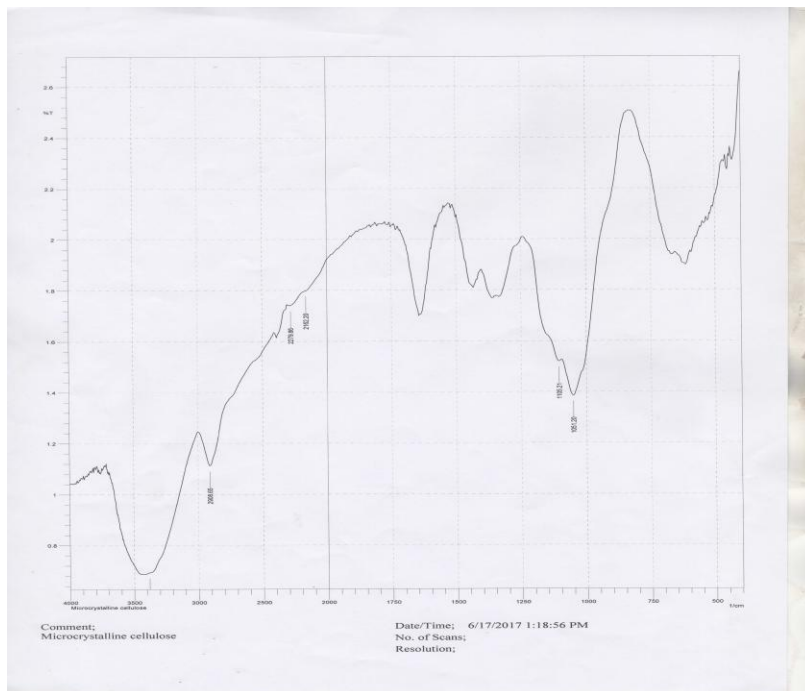
Appendix 2: IR Spectrum of Binary Mixture of Sildenafil and Mannitol



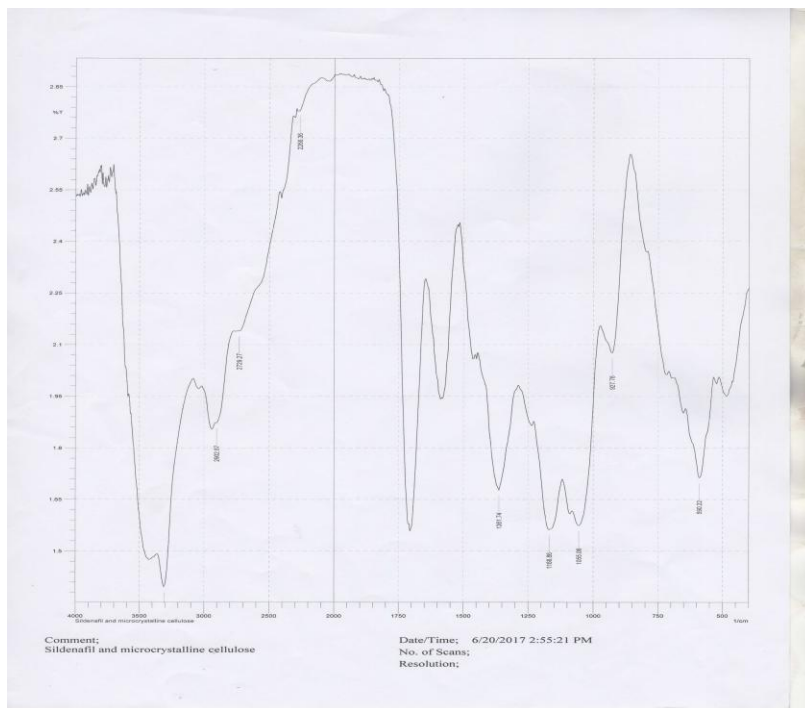
Appendix 3: IR Spectrum of Colloidal Silicon Dioxide



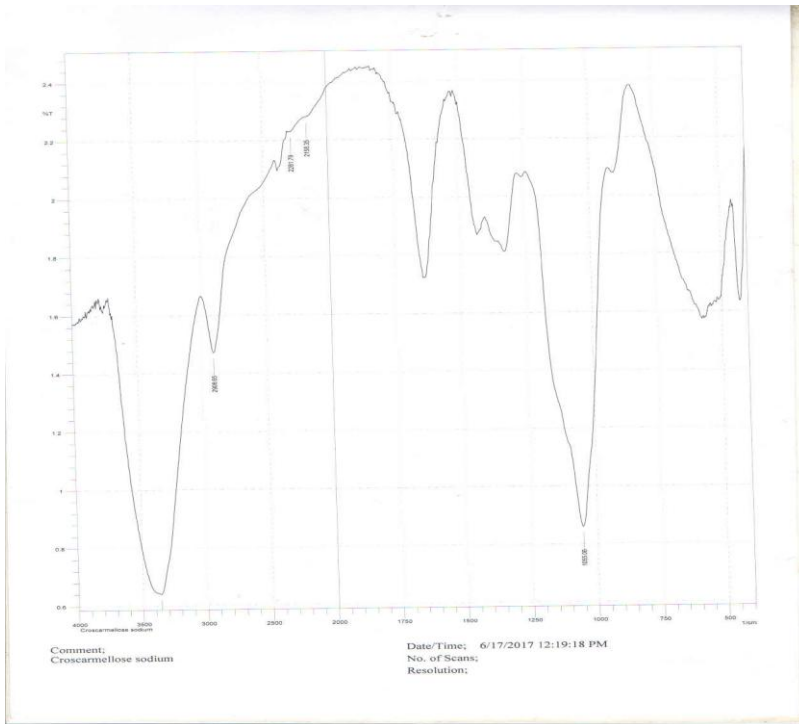
Appendix 4: IR Spectrum of Binary Mixture of Sildenafil and Colloidal Silicon Dioxide



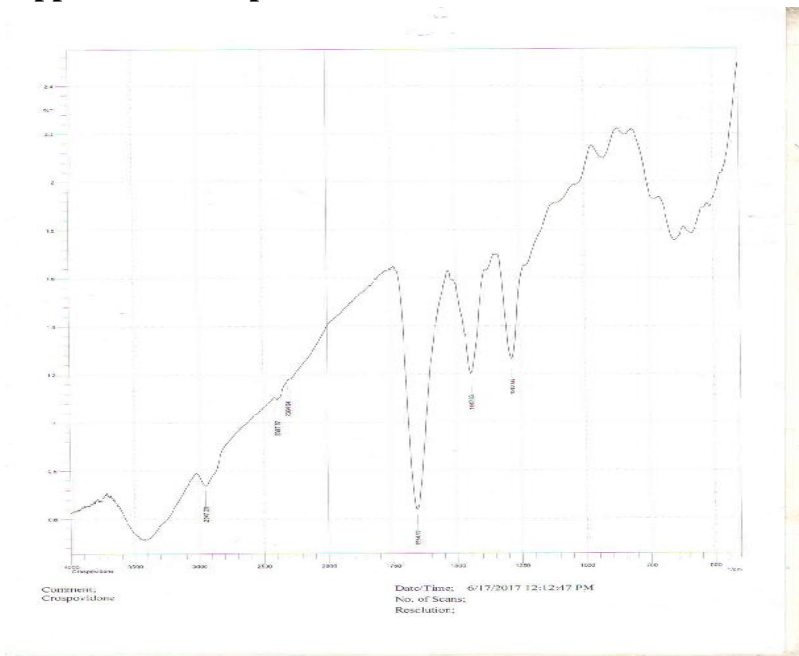
Appendix 5: IR Spectrum of Microcrystalline Cellulose



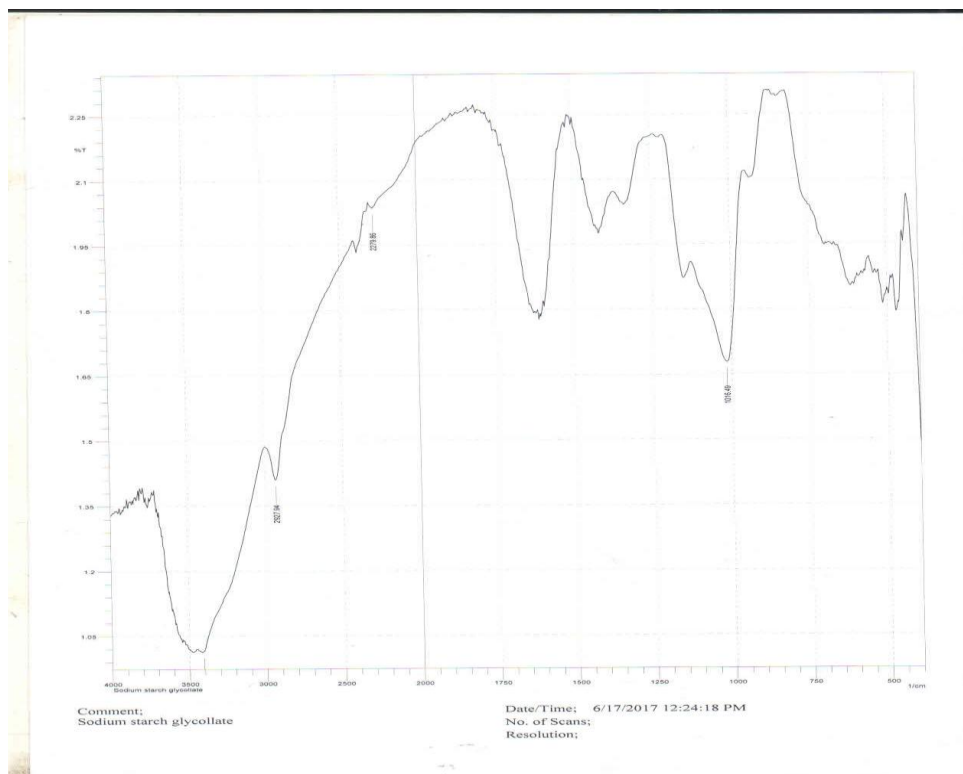
Appendix 6: IR Spectrum of Binary Mixture of Sildenafil and Microcrystalline Cellulose



Appendix 7: IR Spectrum of Crosscarmellose Sodium



Appendix 8: IR Spectrum of Crospovidone



Appendix 9: IR Spectrum of Sodium Starch Glycolate

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Appendix 10: USP 29 Scale Of Flowability

Flow Property	Angle of Repose
Excellent	25-30
Good	31-35
Fair- Aid not needed	36-40
Passable- May hang up	41-45
Poor- Must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Appendix 11: Flow Properties According to Angle of Repose