FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED CHEWABLE TABLET 0F SILDENAFIL CITRATE

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,
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In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

By

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OCTOBER – 2017.

CERTIFICATE

This is to certify that the investigation described in the dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED CHEWABLE TABLET OF SILDENAFIL CITRATE"** submitted by **Reg.No:261510402** was carried out in the Department of Pharmaceutics, **Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil-626 126,** which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the supervision and guidance of **Mr.V.Sivakumar M.Pharm.,(Ph.D)** Associate Professor, Department of Pharmaceutics for the partial fulfillment of degree of MASTER OF PHARMACY in PHARMACEUTICS.

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EVALUATION CERTIFICATE

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"TALENT AND CAPABILITIES ARE OF COURSE NECESSARY BUT OPPORTUNITIES AND RIGHT GUIDANCE ARE TWO VERY IMPORTANT BACKUPS WITHOUT WHICH NO ONE CAN CLIMB THE LADDER TO SUCCESS".

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LIST OF ABBREVIATIONS

S.NO	Abbreviations	Expanded Terminology
1.	NCE	New chemical entity
2.	CNS	Central nervous system
3.	GPCRS	G-protein coupled receptors
4.	CMT	Continuous multipurpose melt Technology
5.	GIT	Gastro Intestinal Tract
6.	IER	Ion Exchange Resin
7.	FTIR	Fourier Transform Infrared Radiation
8.	Kg	Kilogram
9.	Mg	Milligram
10.	µg	Microgram
11.	RH	Relative Humidity
12.	Nm	Nano meter
13.	C	Centigrade
14.	Gms	Grams
15.	Q	Quantity
16.	Mins	Minutes
17.	Sec	Second
18.	Mm	Milli meter
19.	Gm	Gram
20.	Ml	Milli liter
21.	Rpm	Rotation per minute
22.	PDE	Phosphodiesterase
23.	UV	Ultra Violet
24.	CCS	Cros Caramellose Sodium
25.	PVP	Poly Vinyl Pyrolidine
26.	%	Percentage
27.	Fig	Figure
28.	FDA	Food And Drug Administration
29.	USP	United state pharmacopeia

30.	WHO	World Health Organization
31.	ICH	International Conference for Harmonization
32.	API	Active Pharmaceutical Ingredient

CONTENTS

CHAPTER I
INTRODUCTION

1.INTRODUCTION

1.ORAL SOLID DOSAGE FORMS

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of these reason when ever New chemical entity (NCE) has discovered, which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by oral route or not. As a natural defence mechanism to prevent infection or dehydration many trees and shrubs are known to produce an aqueous thick exudation when the plants bark is injured. Eventually the solution dries up in contract with sunlight and air and a hard transparent brown-tint glass mass formed. This solid mass is known as Natural gum[1]. Excipients play an important role in dosage forms such as tablet, capsule, lotions, suspensions, syrups and ointments. Plant products serve as an alternative to synthetic products because of its local accessibility, environment friendly nature and low prices compared to imported synthetic products[2]. *Plantago ovata* mucilage has been evaluated in fast disintegrating tablet.*Ocimum americanum* Linn. Mucilage has been evaluated in disintegrating tablet[3]. Moringa gum is obtained from the tree Moringa Oleifera. Which is a water soluble gum extrudes from the bark on Moringa trees. In present study, an attempt was made to prove Moringa gum as disintegrant. The oral route of administration still continues to be the most preferred route due to its manifold advantages including:

- Tablets and capsules represent unit dosage forms in which the accurate dose of drug to show sufficient pharmacological action can be administered. In case of liquid oral dosage forms such as Syrups, Suspensions, Emulsions, Solutions and Elixirs the patient is asked to administer the medication of 5-30 ml. Such dosage measurements are typically error by factor ranging from 20-50 %, when the drug is self administered by patient.
- Solid dosage forms are less expensive to shipping and less prone for the degradation when compared to liquid dosage forms[4].

1.1.TABLETS

In 1843, the first patent for a hand operated device used to form a tablet was granted. Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They are intended for oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in water before being administered and some are retained in the mouth, where the active ingredient "liberated". Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity and economy of preparation, stability and convenience in packing, shipping and dispensing] and the patient [e.g. accuracy of dosage, compactness, portability, blandness of taste and ease of administration].

They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration. They may have lines or break-marks and may bear a symbol or other markings. Tablets may be coated.

1.1.1. Advantages of Tablets

The primary potential advantages of tablets are,

- ❖ They are the unit dosage forms, which offer the great capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- ❖ The cost is lower of all oral dosage forms.
- ❖ They are the lightest and most compact of all.
- ❖ They are in general the easiest and cheapest to packaging and shipment.
- ❖ Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- ❖ They may provide the greatest case of swallowing with the least tendency for hang up above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.
- ❖ They lend themselves to certain special profile products, such as enteric or delayed release products.
- ❖ They are better suited to large scale production than with other unit oral dosage forms.
- ❖ They have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms.

1.1.2. Disadvantages

In spite of all these advantages, tablet also possesses some disadvantages. The disadvantages of tablets include the following

- ❖ Some drugs resist compression in to dense compacts, owing to their amorphous nature or flocculent, low density character.

- Drugs with poor wetting properties, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drug with obnoxious odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression / coating[4, 5, 6].

1.1.3. PRINCIPLES OF DOSAGE FORM DESIGN

Drugs are rarely administered slowly as pure chemical substances, but are almost given as formulated preparations. The principle objective of dosage form design is to achieve a predictable therapeutic response to a drug included in the formulation. Before a drug substance can be successfully formulated in to a dosage form, many factors must be considered. These factors can be broadly grouped in to three categories.

- Biopharmaceutical considerations (Factors affecting absorption of drugs)
- Drug related factors (Physical and chemical properties of a drug)
- Therapeutic considerations (Disease to be treated and patient factors)

Among various orally administered dosage forms (tablets, capsules, syrup, solution etc), the tablet dosage form is the most widely used.[7, 8]

Compressed tablets are defined as solid dosage forms made by compaction of the formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product.

1.2.1 CLASSIFICATION OF TABLETS

I. Classification based on mode of administration.

1) Chewable tablets
2) Tablets to be swallowed
3) Tablets used in oral cavity

- ❖ Buccal tablets
- ❖ Sublingual tablets
- ❖ Troches and lozenges
- ❖ Dental cones

1)Tablets administered other than oral route

- ❖ Implants
- ❖ Vaginal tablets / suppositories

II. Classification based on drug manufacturing process.

1) Standard compressed tablets
2) Multiple compressed tablets

- ❖ Compression-coated tablets
- ❖ Layered tablets

1) Coated tablets
2) Molded tablets (Tablet triturates)

III. Classification based on drug release profile.

1) Fast dissolving tablets
2) Immediate release tablets
3) Controlled Release tablets (Sustained Release Tablets)
4) Delayed Release tablets (Enteric coated tablets)

IV. Tablets used to prepare solutions.

- ❖ Effervescent tablets.
- ❖ Dispersible tablets.

1.2.2. CHEWABLE TABLET

Chewable tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing.[9]

These tablets are intended to disintegrate smoothly in mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste. Successful tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipient to perform a specific function in a tablet formulation such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic are one type of functional excipient commonly used in chewable tablet formulations to mask the unpleasant tastes and facilitate pediatric dosing. [10,11] Ideally upon chewing, they are broken down in the mouth and release their ingredients in the process and therefore, do not have much lag time as required for the disintegration of tablets before absorption from stomach. [12] Chewable tablets are often employed when the active ingredient is intended to act in a localized manner rather than systemically.

Chewable tablet is one that is palatable and may be chewed and ingested with little or no water. Manufacturing of chewable tablet is generally done using either wet granulation process or direct compression. Increasingly, micronized and submicron

forms of therapeutically and physiologically active substances are incorporated into tablet formulation to take advantage of the enhanced absorption characteristics of these forms. [13] They are also used in the administration of antacids and carminatives. Mannitol is widely used as an excipient in chewable tablet for its non-hygroscopic nature for moisture sensitive drugs. As we know difficulty in swallowing (Dysphasia) is common among all age groups, especially in elderly and in also seen of swallowing of conventional tablets and capsules. Geriatric and pediatric patients and travelling patients who may not have ready access to water are most need of easy swallowing dosage forms like chewable tablets. The composition of chewable tablet consists of gum core, which may or may not be coated. The core is composed of an insoluble gum base like fillers, waxes, antioxidants, sweeteners, flavouring agents. The percentage of gum base varies from 30-60% depending upon the base used and its properties. A flavouring agent is included to make it more palatable.

1.2.3 Advantages of chewable tablets[14, 15]

Chewable tablets are generally chewed in the mouth prior to swallowing and are not expected to swallow intact. The main purpose of a chewable tablet is to provide proper unit dosage forms of medication which can easily to administer to children or to the elderly who have difficulty in swallowing a tablet intact. The chewable tablet has some specific advantages.

- Better bioavailability through by passing disintegration (increase dissolution).
- Improved patient acceptance (especially pediatric) through pleasant taste patient convenience, need no water for swallowing.
- Possible to use as a suitable for liquid dosage forms where rapid onset of action is needed adsorption of the drug is faster product distinctiveness through marketing perspective.

- The large size of the dosage forms is difficult to swallow.
- In such case, chewable tablets offer effectiveness of therapeutic agent is improved by the reduction in size that occurs during mastication of tablets before swallowing.

1.2.4 Disadvantages of chewable tablets

There are of course some limitations to the use of chewable having bad tasting drug and extremely high dose level.

- It contains sorbitol which causes diarrhea and flatulence flavoring agents present in a chewable tablet may cause an ulcer in the oral cavity.
- Prolonged chewing of chewable tablets results in pain in facial muscles.
- They are hygroscopic in nature, so must keep in a dry place they slow the fragile, effervescence granules property. Since they tablets having insufficient mechanical strength. So careful handling is required.

1.2.5. METHOD OF MANUFACTURING [16, 17, 18]

The chewable tablets were prepared by using the following method.

1. Non-aqueous granulation/dry granulation.
2. Aqueous granulation/wet granulation
3. Direct compression.

- **Granulation**

Granulation is the process in which primary powder particles are made to adhere to form larger, multi-particles entities Called granules. Pharmaceutically granules have a size range between 0.2 to 4.0 mm .granulation is used to improve flow and compressibility of the powders and segregation of the blend compounds. Granulation is mainly done by using two techniques.

1. Dry granulation

It is a novel method for semi-automatic production of granules. the method is applicable to any solid dosage for pharmaceuticals products.dry granules method replace existing solid dosage form development and manufacturing technology offering more rapid. in the process, the powder mixture is compressed without the use of heat and solvent. two methods are used for dry granulation. The more widely used slugging where the powder is recompressed and resulting tablet is milled to yield the granules.

2. Wet granulation

Wet granulation is the most commonly used granulation method. This process involves wet massing powder blend with a granulating liquid, wet sizing, and drying. It can be removed from the volatile materials. That it can be removed drying and most be Non-toxic in nature. The typical liquid includes water, ethanol and isopropyl alcohol. in this traditional wet granulation method, the wet mass is forced through the sieve to produce wet granules which are subsequently dried.

3. Direct compression

Direct compression is the most popular choice because it provides the shortest. Most effective and least complex to produce tablets. This method has mainly used a group of ingredients can be blended. This is more suitable for moisture and heat sensitive API's since it eliminates wetting and drying steps and increases the stability of active ingredient by reducing to detrimental (Harmful) effects. In the process of API mixed with the excipients and lubricants, followed by compression.

1.2.6. Mechanism of action of chewable tablets[19, 20]

Chemoreceptor's on the tongue

Taste is brain interpretation of chemicals triggers on the tongue. This is on taste buds. Molecules interact with taste receptors on the tongue to taste sensation .This sensation is the result of signal transudation from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, when there dissolve in the saliva. Which produce and transmit an electrical impulse to the seventh, ninth, tenth to the area of the brain.

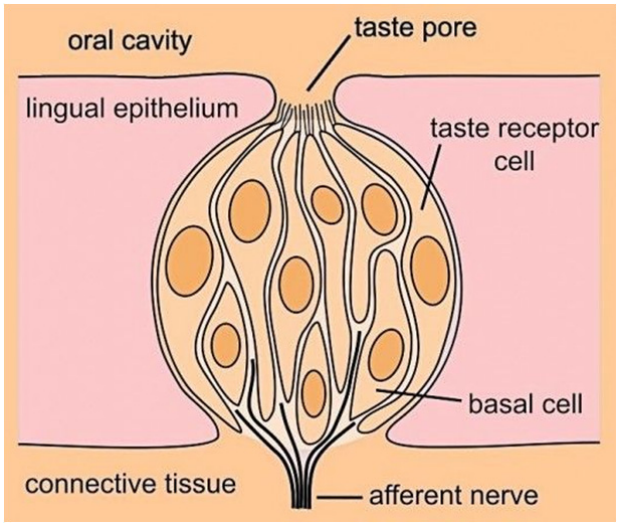


Figure no.1. Taste buds in cell Structure

1.2.7. PHYSIOLOGY OF TASTE

The sense of taste is mediated by taste bud, which is a group of taste receptor cell (50-100 cells), bundled in a cluster like bannans and gives a sensation of taste via sensory neurons to central nervous system (CNS) in the brainstem. Taste buds are chemoreceptor stimulated by chemicals dissolved in saliva from oral ingested medicaments and enter via the taste pore followed by interaction with surface proteins known as taste receptors causing electrical change within taste cells, which cause the transmission of signals to the brain.

Four fundamental sensations of the taste have been described.

1. Sweet. (Sugar, glycerol)
2. Salty. (Sodium)
3. Bitter. (Quinine, nicotine)
4. Sour. (Acidic substance)

1. SALTY TASTE (EDGE, UPPER PORTION)

Salty taste is one of the four receptors of the tongue; they are located on the edge and upper front portion of the tongue.

2. SWEET TASTE (TIP)

The sweet taste is one among the four taste receptors in the tongue. There are found on tip of the tongue.

3. SOUR TASTE (ALONG SIDES IN BACK)

The sour taste is also one of the four taste receptors of the tongue. They occur at sides of the tongue and are stimulated mainly by acids.

4. BITTER TASTE (BACK) [21]

The bitter taste is the last and one of the four taste receptors on the tongue. That is located towards the back of the tongue. It is stimulated by a variety of chemicals substances, most of which are organic compounds, although some inorganic compounds such as magnesium and calcium also produce bitter sensations.

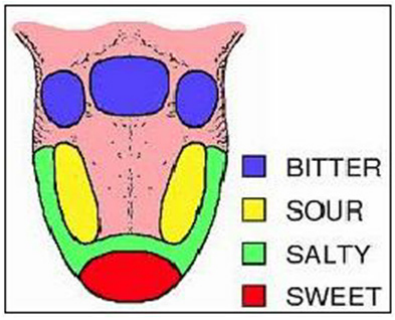


Figure no.2. Taste buds

1.3. TASTE SIGNALS PATHWAYS [22]

Taste transduction begins with the interaction on the taste. (eg. medicine, food) with taste receptors cells in taste buds. The tastant binds with g-protein coupled receptors (GPCRS) cells triggering the release of the G-protein called gustducin.the process of taste sensation begins when gustducin activates the effector enzymes phosphodiesterase IA (PDE) or phospholipase C BETA-2(PLC).the effectors enzymes then change the intracellular level second messengers such as cyclic adenosine monophosphate ($_C$AMP),Inositol, 1,4 ,5 –triphosphate(IP3) and diacylglycerol (DAG).the second messengers Activate ion channel including calcium channel on the extra cellular membrane. This ionization depolarizes the cell causing the release of neurotransmitters that send a nerve impulse to the brain that carries the signal of bitter taste and taste blockers work by interfering with taste transduction.

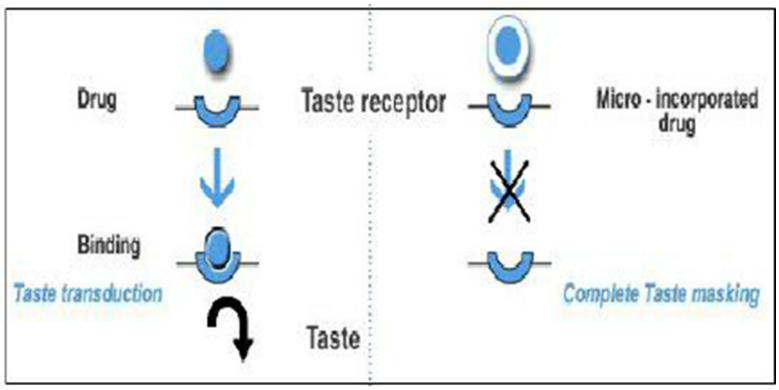


Figure no.3. Taste signal pathways

1.3.1. TASTE BLOCKING MECHANISM [23]

Taste sensation begins with gustducin activates the effectors enzyme phosphodiesterase IA (PDE)phospholipase C beta-2(PLC).the effectors enzyme then change the intracellular level of second messengers such as cyclic adenosine monophosphate (cAMP)1,4,5-triphosphate (IP3)and diacylglycerol(DAG).the second messengers active calcium ion channel inside the cell neurotransmitters to the nerves.

Impulse transmits into the brain bitter taste and taste blockers work by interfering with taste transduction.

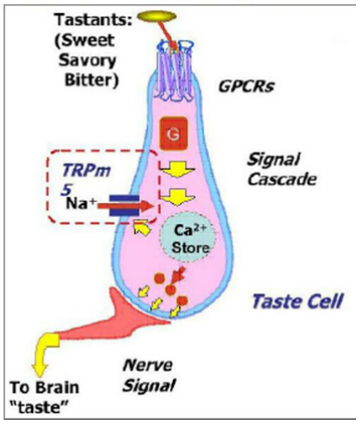


Figure no.4. Taste blocking mechanism

1.3.2. TASTE MASKING TECHNOLOGY

Taste masking is defined as perceived reduction of an undesirable taste that would otherwise exist. [24]Methods commonly used for the two types.

1. The chemical method that prevents from the interaction of taste buds with drugs.
2. Physical method.

1.3.3. TWO APPROACHES BASED ON THE BAD TASTE OF THE DRUG

1. By reducing the solubility of drug in the PH of the saliva (5.6-6.8)
2. By altering the affinity and nature of drug will interact with receptors.[25]

1.3.4. AN IDEAL TASTE MASKING PROCESS AND FORMULATION SHOULD HAVE THE FOLLOWING PROPERTIES

1. Involve the least number of equipment and process.
2. Effectively mask the taste with as few Excipients .which are economically and easily available.
3. No adverse effect on the drug bioavailability.

4. Least manufacturing cost.
5. Can be carried out room temperature.
6. Require excipients that have a high margin of safety.
7. Rapid and easy to prepare.

1.3.5. FACTORSCONSIDERATION DURING THE TASTE MASKING FORMULATION PROCESS INCLUDES

1. The extent of the bitter taste of the API.
2. Required dose load.
3. Drug particulate shape and size distribution.
4. Drug solubility and ionic characteristics.
5. Required disintegration and dissolution rate of the finished product.
6. desired bioavailability.
7. Desired release profile.
8. Required dosage forms.

1.3.6. TASTE MASKING TECHNOLOGIES[26]

To achieve the goal of taste abatement of the bitter or unpleasant taste of the drug. The various methods involved.

1. Taste masking with flavors, sweeteners& amino acids.
2. Taste masking by granulation.
3. Taste masking by Microencapsulation.
4. Ion Exchange Resins.
5. Taste masking by formulation of inclusion complexes.
6. Taste masking by Prodrug approach.
7. Solid dispersion system.

8. PH Modifiers.
9. Taste masking by adsorption.
10. Taste masking by relation.
11. Multiple Emulsions.
12. Development of Liposome.
13. Miscellaneous taste masking approaches
    - By effervescent agents
    - Rheological modification
    - Continuous multipurpose melt (CMT) Technology

1.Tastemaskingwithflavours,sweetners,andaminoacids

This technique is simplest approach taste masking. But this technique was not very successful for highly bitter taste drugs taste masking failure. Artificial sweeteners and flavors are generally being used alone with other taste masking techniques to improve the efficiency of taste.

A.)Flavors

1.) Complementary to existing of the flavor of the drug.

2.) The known popularity of particular flavors.

3.) Allergy

4.) Age of patients.

Natural vs. synthetic:

- ❖ Cheaper.
- ❖ More readily available.
- ❖ Less variable in chemical composition.
- ❖ More stable flavoring agents for taste masking.

Natural flavors	**:**	Raspberry juices; Liquorices.
Extract	:	lemon orange spirits
Syrup	:	ginger tinctures: anise cinnamon aromatic.
Water	:	peppermint lemon aromatic oils.
Synthetic flavors	:	alcoholic solution: aqueous solutions: powders

B.)Sweeteners

1. Complement flavors associated with sweetness
2. Soothing flavors associated with the throat.

Natural sweetener - sucrose, glucose, fructose, mannitol.

Artificial sweeteners - saccharin, saccharin sodium, aspartame.

Nutritive sweeteners - sucrose, fructose, glucose.

Non-nutritive sweeteners- Aspartame, sucralose, Neotame, Saccharine.

Polyols - mannitol, sorbitol, xylitol, maltitol.

Novel sweeteners - Trehalose, tagatose.

C. Amino acids

Amino acids and they're (alanine, taurine, glutamic acid, glycine) in combination with bitter drugs reduce the drug. Ampicillin improved markedly by preparing its granules with them with an additional quantity of glycine, sweeteners, flavors and finally compressing them into tablets.

2. Taste masking by granulation

Granulation is a less expensive, rapid operation and an easily scalable taste masking technology. This step can be exploited as a mean for taste masking of slightly bitter tasting drug. Granulation lowers the effective surface area of the bitter substance that come in contact with the tongue upon oral intake. Liquid and low

melting point waxes such as glycerol palmitostearate, glyceryl behenate and hydrogenated castor oil are commonly used ingredients during the granulation to achieve taste masking.

3. Taste masking by microencapsulation

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a film or polymeric material. Coating is an extremely useful technique for a number of applications in pharmaceutical field. Although it is used primarily for production of sustained release, Gastro-intestinal dosage forms, it also has major applications in masking the unpleasant taste. It is important to understand that only soluble portion of the drug can generate the sensation of taste. Coating the active drug with a properly selected polymer film can reduce its solubility in saliva and thus taste could be masked. Coating the drug particles created a physical barrier between the drug and the taste buds and taste of active could be masked. The goal of Microencapsulation may be accomplished by any of the following techniques.

- Air suspension coating
- Spray drying and spray congealing
- Coacervation - phase separation
- Solvent evaporation
- Multiorifice - centrifugal process
- Pan coating
- Interfacial polymerization

Polymers used for coating in microencapsulation

Coating is an extremely useful technique for number of applications in the pharmaceutical field. It is classified based buds. Cyclodextrin is most widely used

complexing agent for inclusion type complexes. It is sweet, non toxic, cyclic oligosaccharide obtained from starch. The following are the examples of drugs that the bitter taste can be suppressed by making inclusion complexes.

4. Ion exchange resins

Ion exchange resins (IER) have received considerable attention from pharmaceutical scientists because of their versatile properties as drug delivery vehicles. In past few years, IER have been extensively studied in the development of Novel drug delivery system and other biomedical applications. Several ion exchange resin products for oral and peroral administration have been developed for immediate release and sustained release purposes. Bitter tasting drugs can be absorbed onto ion exchange resins, thus effectively removing them from solution during the transit through the mouth, at salivary pH 6.8, remains in intact form making the drug unavailable for the taste sensation. Various studies have revealed that ion exchange resins are equally suitable for drug delivery technology. Some ion exchange resins used widely for taste masking purpose in industries are Amberlite IRP64, Amberlite IRP69, Indion 204, Indion 214, Kyron T-114 and Kyron T-104.

5. Taste masking by formulation of inclusion complexes

Inclusion complexation is a process in which the guest molecule is included in the cavity of a host or complexing agent. The complexing agent is capable of masking bitter taste of drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste.

6. Taste masking by prodrug approach

Chemical modification, including prodrug design is an effective method for reducing solubility, and thereby improving taste. A prod rug is chemically modified

inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound. Bitterness of a molecule may be due to the efficiency of the taste receptor substrate adsorption reaction, which is related to the molecular geometry of the substrate. If alteration of the parent molecule occurs by derivative formation, the geometry is altered, affecting the adsorption constant. Thus the magnitude of a bitter taste response or taste receptor-substrate adsorption constant may be modified by changing the molecular configuration of the parent molecule. The extremely bitter antibiotics have been the focus of much work in reversible drug modification. Taste masking of drug.'

7. Solid dispersion system

Solid dispersion has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method. Recently solid dispersions were introduced as a taste masking technology. Tsau and Damani (1994) disclosed a drug-polymer matrix composition to achieve the taste masking of dimenhydrinate. Amine or amide group of dimenhydrinate can have a physical and chemical interaction with the carboxylic acid and esters groups of copolymers such as shellac, zein and cellulose acetate phthalate hydrophobic polymers and long chain fatty acids have been used to achieve the taste masking by solid dispersion. This approach usually requires a higher concentration of excipients compared to other taste masking techniques. Natural polymers such as shellac and zein, and enteric polymers like derivatives of acrylic acid polymers and phthalate are good choices to develop the taste masked solid dispersions.

8. Ph modifiers

Many natural and synthetic polymers, resins and waxes alone or in combinations have been employed for taste masking. The enteric polymers like eudragit L are used for taste masking but the pH of saliva is near 5.8 and these polymers solubilize at pH beyond 5.5 so there is a possibility of drug being partially leached. Therefore there is a need for the development of taste masking polymer such that the bitter taste is completely masked by the polymer at the pH of saliva in mouth and in the reconstitution medium as in case of the liquid orals and further which is able to protect the drug in a biologically active form, from the moisture in the dosage form and releasing the drug rapidly in the stomach without affecting its absorption and bioavailability. Developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption. The formulation contains the drug in combination with effervescent agent to promote their absorption in the oral cavity and to mask their bitter taste. An additional pH adjusting substance was also included in fentanyl formulation for further promotion for absorption.

9. Taste masking by adsorption

Adsorbates are commonly used in taste masking technologies. Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will absorb the drug, removing the solvent, drying the resultant powder, and then using these dried adsorbates in the preparation of the final dosage form. Many substrates like veegum, bentonite, silica gel and silicates can be used for the reparation of Adsorbate of bitter drugs. The bitter taste of ranitidine is masked by forming an adsorbate with a synthetic cation exchange resin.

10. Taste masking by gelation

Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking. Sodium alginate has the ability to cause water insoluble gelation in presence of bivalent metal ions. Tablet of amiprolose hydrochloride have been taste masked by applying a undercoat of sodium alginate and overcoat of calcium gluconate. In presence of saliva, sodium alginate reacts with bivalent calcium and form water insoluble gel and thus taste masking achieved.

11. Multiple emulsions

A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability. The formulation is designed to release the drug through the oil phase in the presence of gastrointestinal fluid.

12. Development of liposome

Another way of masking the unpleasant taste of therapeutic agent is to entrap them into liposome. For example, incorporating into a liposomal formulation prepared with egg phosphatidyl choline masked the bitter taste of chloroquine phosphate in HEPES (N-2-hydroxyetylpiperzine-N'- 2- ethane sulfonic acid) buffer at pH 7.2.

13. Miscellaneous taste masking approaches

- **By effervescent agents**

Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration. A chewing gum composition of bitter medicament was formulated to supply the medicament to oral cavity for local application or for buccal absorption. It comprise a chewing base, an orally administrable medicament, a taste masking generator of carbon dioxide, and

optionally a taste bud desensitizing composition (e.g., oral anesthetic such as benzocaine) and other non active material such as sweeteners, flavoring components, and fillers. Recently, effervescent tablets of fentanyl and prochlorperazine were located and dissected from the surrounding tissue and cut proximally. An ac-amplifier and an electronic integrator are used to respectively amplify and integrate the nerve impulses. The peak height of the integrated response is then taken as the magnitude of response.

- **Rheological modification**

Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. Acetaminophen suspension can be formulated with xanthan gum (0.1-0.2%) and microcrystalline cellulose (0.6-1%) to reduce bitter taste. The antidepressant drug mirtazapine is formulated as an aqueous suspension using methonine (stabilizer) and maltitol (thickening agent). Maltitol is stable in the acidic pH range of 2 to 3 and besides masking the unpleasant taste of the drug, it also inhibit its undesirable local anesthetic effect .

- **Continuous multipurpose melt (cmt)technology**

The CMT method was developed for the continuous granulation and coating of pharmacologically active substances. It was concluded that this method could be successfully applied for taste masking of bitter drug.

1.3.7 Criteria for selection of chewable tablets

Chewable tablets must be chewed before swallowing and typically contain a combination of colors, flavors, and sweeteners. This tablet form is suitable for ingredients with neutral or sweet flavor or tablets that contain a large amount contain a lot of active ingredients that do not lend themselves to being swallowed whole.

CHAPTER II
LITERATURE REVIEW

2. LITERATURE REVIEW

S.V.Sai kumar et al., (2010) The aim of this work was to develop and validate simple, accurate and precise spectroscopic methods (multicomponent, dual wavelength and simultaneous equations) for the simultaneous estimation and dissolution testing of ofloxacin and ornidazole tablet dosage forms. The medium of dissolution used was 900 ml of 0.01N HCl, using a paddle apparatus at a stirring rate of 50 rpm. The drug release was evaluated by developed and validated spectroscopic methods. Ofloxacin and ornidazole showed 293.4 and 319.6nm as λ_{max} in 0.01N HCl. The methods were validated to meet requirements for a global regulatory filing. The validation included linearity, precision and accuracy. In addition, recovery studies and dissolution studies of three different tablets were compared and the results obtained show no significant difference among products[44].

B.Sree giri Prasad et al., (2013) The objective of the present study is to develop chewable tablets containing different pharmaceutical compositions with simple manufacturing procedures using different excipients. Mannitols, L-HPC 11, Aspartame, Crospovidone, Crospovidone, Aerosil, and Magnesium Stearate are used as excipients for effective formulation of anti-asthmatic drug Montelukast. Montelukast chewable tablets were prepared by both wet granulation and Direct Compression methods using suitable excipients. The chewable tablets were better presented using artificial sweetener Aspartame as flavouring agent. A total of eight formulations were prepared and the granules were evaluated for pre-compression parameters. The formulated tablets were evaluated for post-compression parameters. The results showed that all the physical parameters were within the acceptable limits. I.R spectral studies revealed that there was no interaction between the drug and

excipients. The in vitro release study of formulation F_7 showed 98.85%drug release at the end of 30 min. The stability studies for the formulation F_7 showed no significant changes and the study concludes that formulation F_7 showed better characteristics of chewable tablet[45].

Bhupendra kumar poudel et al., (2014) The objective of the present study is to develop chewable tablets containing different pharmaceutical compositions with simple manufacturing procedures using different excipients. Mannitols, L-HPC 11, Aspartame, Crospovidone, Crospovidone, Aerosil, and Magnesium Stearate are used as excipients for effective formulation of anti-asthmatic drug Montelukast. Montelukast is a selective, orally acting leukotriene receptor antagonist that is used for the treatment of asthma and seasonal allergic rhinitis. Montelukast chewable tablets were prepared by Direct Compression methods using suitable excipients. The chewable tablets were better presented using artificial sweetener Aspartame as flavouring agent. A total of forteen formulations were prepared and the granules were evaluated for pre-compression parameters. The formulated tablets were evaluated for post-compression parameters .The results showed that all the physical parameters were within the acceptable limits. The in vitro release study of all the formulations showed good release. The study concludes that aforementioned excipients can be used to design chewable montelukast sodium tablets[46].

V.Anusha et al., (2012) Albendazole chewable tablets were prepared by wet granulation method. Using two superdisintegrants such as croscarmellose sodium and sodium starch glycolate. A total of eight formulations were prepared and the granules were evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The formulated tablets

were evaluated for diameter, thickness, hardness, weight variation, friability, disintegration and drug content. The results showed that all the physical parameters were within the acceptable limits. IR spectral studies revealed that there was no interaction between the drug and excipients. The in vitro release study of formulation F8 showed81.03%drug release at the end of 30 min. The stability studies for the formulation F8 showed no significant change in disintegration time, drug content and percentage drug release after stored at 40o±2oC/75±5%RH for a period of30 days. Hence the study concludes that formulation F8 showed better characteristics of chewable tablet[47].

Bharat Parashar et al., (2012) Albendazole is a benzimidazole derivative with broad spectrum anthelmenthic activity and excellent tolerability. Orally it is rapidly absorbed and metabolized to sulfoxide and sulfone, which may be responsible for its anthelmenthic action. Single dose administration of albendazole has produced cure rates in ascarisis, hookworm and enterobiasis which are comparable to three day treatment with mebendazole. Albendazole chewable tablets (400 mg) were prepared by three methods *viz.* non aqueous granulation, aqueous granulation and direct compression and were named as NAG, AG and DC respectively. Tablet prepared by these three methods were evaluated by different parameters such as average weight, hardness, Carr's index, tapped density, friability, disintegration, content uniformity test, *in vitro* dissolution *etc.* All the parameters were found within the specifications. The study on the dissolution profile revealed that product 'DC' had faster dissolution rate while compared to remaining batches and marketed product. Assay values were within the limits of 90% to 110%[48].

V.Gopal et al., (2012) various formulations of Loratadine Chewable tablets containing different pharmaceutical compositions with simple manufacturing procedures were developed by using different excipients. The excipients used here are Lactose, Mannitol, Ethyl cellulose, microcrystalline cellulose, Maize Starch, Citric Acid, Aspartame, Colloidal silicon dioxide, Magnesium Stearate, D & C Yellow No 10 and Raspberry flavour. Oral chewable tablets are the most preferred among the conventional dosage forms due to its aesthetic appeal and ease of administering to children, which has entered the market. The chewable tablet was better presented using artificial sweetener Aspartame and Raspberry flavour as flavouring agent. The tablets were evaluated for weight variation, hardness, friability; drug content and mouth feel along with *in-vitro* dissolution. As per monograph, the chewable tablets are not required to comply with disintegration test. Wet granulation process using Mannitol, Lactose, Micro crystalline cellulose (Avicel-CE 15), Ethyl cellulose and Sweeteners and Flavours were found to be simple and robust method to prepare chewable tablets[49].

M.Rajesh et al., (2012) Albendazole chewable tablets were prepared by wet granulation method. Using two superdisintegrants such as croscarmellose sodium and sodium starch glycolate. A total of eight formulations were prepared and the granules were evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The formulated tablets were evaluated for diameter, thickness, hardness, weight variation, friability, disintegration and drug content. The results showed that all the physical parameters were within the acceptable limits. IR spectral studies revealed that there was no interaction between the drug and excipients. The in vitro release study of formulation F8 showed81.03%drug release at the end of 30 min. The stability studies for the

formulation F8 showed no significant change in disintegration time, drug content and percentage drug release after stored at 40o±2oC/75±5%RH for a period of30 days. Hence the study concludes that formulation F8 showed better characteristics of chewable tablet[50].

Mohit kumar et al., (2014) Formulation of chewable tablet of amoxicillin potassium clavulanate and perform the in vitro bioequivalence study with trying to enhance the bioavailability of innovator formulation. chewable tablet are given to the adults who dislike swallowing and to children who difficulty in swallowing and total 10 formulation were made with different concentration of microcrystalline cellulose & crosscarmellose sodium .the formulation were evaluated for weight variation,hardness,friability data indicates good mechanical resistance of the tablet. All tablet disintegrate in between 3-5 min.the optimized the formulation showed good disintegration time and release profile maximum drug being release marketed preparation at all time intervals[51].

Y. Kranthi Kumar et al., (2014) In this research study the effect drug release of albendazole chewable tablets has been determined. The drug release is calculated by using disintegration process which is directly related to with the hardness of tablets. The tablets are prepared by using three types of granulating methods are non-aqueous granulation, aqueous granulation and direct compression. The tablets are evaluated by calculating different parameters such as hardness, friability, disintegration, assay and in vitro dissolution studies**.** The % drug release was determined by using U V spectrophotometry. In the three techniques and the non-aqueous granulation was the better technique for the formulation of tablets, dissolution rate and % drug release other than aqueous granulation and direct compression method. So by this we can say

the non- aqueous technique is gives immediate drug release by which the drug can be used at the time of emergency and gives relief to the patient and the chewable tablets can used for the children easily. The present study was to prepare the chewable albendazole tablets by granulating techniques i.e. non aqueous granulation, aqueous granulation and direct compression methods and to compare the drug release profiles of the tablets with the marketed[52].

Swati Jagdale et al., (2010) Levamisole is a synthetic imidazothiazole derivative that has been widely used in treatment of worm infestations in both humans and animals. As an anthelmintic, it probably works by targeting the nematode nicotinergic acetyl-choline receptor. In the market, levamisole tablets are available in the form of tablets. Geriatric and paediatric patients find it difficult to swallow these tablets. So in order to avoid this problem, chewable tablets are most pre-ferable. The chewable tablets of levamisole were prepared by using lactose or mannitol along with sodium starch glycolate in concentration ratios especially for paediatric use. Sodium saccharin and vanilla were used as sweeten-ing agent and flavouring agent respectively. From the disintegration studies, it was observed that the formulation containing 1.6% w/w of sodium starch glycolate shows minimum disintegration time whereas formulation having no or less concentration of sodium starch glycolate shows increase in disintegration time. It was observed that the formulation containing lactose shows less disintegration time than formulation containing mannitol[53].

Huda.i.G et al., (2013) In the present work, chewable dispersible tablets of Pregabalin were designed by preparing taste masked granulates of Pregabalin with Eudragit EPO. The tastes masked granulate was prepared by granulation technique in Rapid Mixer Granulator using Eudragit EPO with a drug: Eudragit EPO ratios 1:0.15,

1:0.2, 1:0.25 and 1:0.3 (% w/w). Assay content and In-vitro decomplexation studies confirmed taste masking of granulate. It was found that maximum taste masking of drug with Eudragit EPO was noted at a ratio of 1:0.25. Drug release from Drug: Eudragit EPO complex in salivary pH imparts slight after bitter taste which was overcome by addition of sucralose during granulation. A study on different flavor is studied to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity and *in vitro* dispersion time. Based on acceptable physical characteristic, formulations were tested for *in vitro* drug release pattern (in 0.06M Hydrochloride) [54].

O.G .Bhusnure et al., (2015) Chewable tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing. These tablets are intended to disintegrate smoothly in the mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste. Many active pharmaceutical ingredients (API) inherently possess a bitter taste. Nearly 20% of American adults surveyed complained of bad aftertastes or struggling to swallow when trying to take medication. The most popular oral dosage forms include liquids, powders, granules, orally disintegrating tablets (ODT), and chewable tablets. For solid oral dosage forms like orally disintegrating tablets and chewable tablets, break-lines can be included in the tablet design to adjust dosing. As a result, chewable tablets has seen an increased interest from the pharmaceutical industry in taste-masking technologies[55]

K.Khar et al., (2004) Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability. This article reviews the earlier applications and methodologies of taste masking and discusses the most recent developments and approaches of bitterness reduction and inhibition for oral pharmaceuticals[56].

Vishnumurthy vummaneni et al., (2012) Taste, smell and texture are the important factors in development of oral dosage forms. Taste is now a factor influencing the patient compliance and product quality. “The worser the taste of the medication, the better the cure” an older attitude which now totally changed. Taste masking of obnoxious drugs has gained the importance as the most of them are administered orally. This reason is an initiative for the development of various taste masking technologies by which the characteristics of the dosage form is improved and good patient compliance is achieved. The main objective of this review is to explore various methodologies for masking the taste of obnoxious drugs, applications, evaluation and also the recent trends in taste masking technologies[57].

Basim Deshmukh et al., (2014) Sildenafil citrate is a pharmacological agent which has proven useful in treatment of erectile dysfunction, pulmonary arterial hypertension as well as high altitude motion sickness. Sildenafil citrate exhibits an absolute bioavaibality of about 40% and is reported to result in maximum observed plasma concentration of about 30-120 minutes following after oral administration. Sildenafil citrate exhibits low water solubility,namely 3.5mg/ml. This low water solubility with its high presystemic metabolism have contributed to its low oral bioavailability. Thus,there is a need to to improve the bioavailability of sildenafil citrate. Fast dissolving tablet of sildenafil citrate were prepared with a intention to gain pre gastric absorption that will eliminate the presystemic metabolism of drug. Attempts were also made to improve the acqueous solubility of the drug by forming its nanocrystals. The nanocrystals of sildenafil citrate were formed by nanoprecipitation technique and were evaluated for particle size and shape by scanning electron microscopy and were also subjected to DSC and FTIR analysis.This formed nanocrystals were further considered as API for the fast dissolving tablet. The formulated F3 formulation(fast dissolving tablet containing cross povidone as polymer and sildenafil citrate nanocrystals) shows rapid drug release within 2 minutes as compared to the tablet containing pure drug[58].

Aditi Tripathi et al., (2011) Taste is an important parameter in case of drugs administering orally. Taste masking becomes a prerequisite for bitter drugs to improve the patient compliance especially in the pediatric and geriatric population. The problem of bitter taste of drug in pediatric formulations is a challenge to the formulators in the present scenario. Masking the bitter taste of drugs is a potential tool for the improvement of patient compliance which intern decides the commercial success of the product. Two approaches are commonly utilized to overcome the bad

taste of the drug. The first includes reduction of drug solubility in the saliva and second approach is to alter the ability of the drug to interact with taste receptor. Various methods are available to mask the undesirable taste of the drugs. Some of them are coating of drug particles, by formation of inclusion complexes, molecular complexes of drugs with other chemicals, solid dispersions, melting method, micro encapsulation, prodrugs, mass extrusion methods and ion exchange resins[59].

Rushiraj Jani et al., (2016) Sildenafil citrate is one of the most effective agents for treatment of erectile dysfunction which acts by inhibiting thecGMP-specific phosphodiesterase type 5. Extensive research work is focused on flash release dosage forms and especially fast dissolving films are successful to attract pharma-industry due to ease of preparation and opportunityto extend patent life. Films are widely acceptable in patients too because of quick onset and user friendliness. Theaim of present study was to prepare fast dissolving films of sildenafil citrate which provides product differentiation from other marketed products and also quick disintegration of highly bitter drug with satisfactory taste masking inoral cavity. Film formulation can be taken within the pocket and patient can take it without need of water by simplyputting it on tongue without any grittiness that is frequently found during disintegration of orodispersible tablets.the formulation will disintegrate within minute and ultimately provides good bioavailability and quickonset. The IR studiesconfirmed complete complexation of drug with taste masking resin. Using experimental design, the preparedformulations were evaluated for in vitro dissolution, solution time and their physicomechanical parameters mainlytensile strength.[60]

Hiren Patel et al., (2012) The present study was undertaken to formulate and evaluate transdermal gel of Sildenafil citrate. Sildenafil citrate is a drug of choice used

in the treatment of premature ejaculation disorder. Transdermal gel has gained more and more importance because the gel based formulations are better percutaneously absorbed than creams and ointment bases. Therefore, transdermal gel of Sildenafil citrate was prepared using different polymers such as carbopol 934P containing permeation enhancer PEG 400 at different proportions. The study encompasses compatibility studies using FTIR spectr*a,* drug content, viscosity, spreadability, and pH determination. Further the optimized formulation evaluated by *in vitro* and *ex vivo* diffusion study. Optimized formulation subjected to stability as well as *ex vivo* study. The preliminary compatibility studies conducted revealed that there was no interaction between Sildenafil citrate and excipients. *In vitro* drug release study was carried out with Franz diffusion cell using cellophane membrane in pH 7.4 phosphate buffers as diffusion medium. Formulation batch containing carbopol 934P and PEG 400 permeation enhancer showed 99.20 % drug release at 180 min and 7.98 g.cm /sec spreadability. Stabilitystudies conducted under accelerated condition were shown satisfactory results. It was concluded that carbopol gel containing Sildenafil citrate showed good consistency, spreadability, homogeneity and stability[61].

S.B.Ahire et al., (2012) Taste is an important parameter in administering drugs orally and is a critical factor to be considered while formulating orodispersible, melt in mouth, buccal tablet and other formulations which comes in contact with taste buds. Good flavor and texture are found to significantly affect sell of the product. Undesirable taste is one of the important formulation problems encountered with most of the drugs. Taste masking technologies offer a great scope for invention and patents. Several approaches like adding flavors and sweeteners, use of lipoproteins for inhibiting bitterness, numbing of taste buds, coating of drug with inert agents, microencapsulation, multiple emulsion, viscosity modifiers, vesicles and liposomes,

prodrug formation, salt formation, formation of inclusion and molecular complexes, solid dispersion system and application of ion exchange resins have been tried by the formulators to mask the unpleasant taste of the bitter drugs. The present review attempts to give a brief account of different technologies of taste masking with respect to dosage form and novel methods of evaluation of taste masking effect[62].

CHAPTER 3
AIM AND OBJECTIVE

3. AIM AND OBJECTIVE

The main aim and objective of this study is to formulate and evaluate chewable tablet of taste masking sildenafil citrate.

3.1. REASON FOR SELECTION OF CHEWABLE TABLETS OF TASTE MASKING SILDENAFIL CITRATE

Clinically selective inhibitor of phosphodiesterase type 5 enzymes (PDE5) is extensively used for the treatment of erectile dysfunction. Conventional sildenafil citrate tablet available in the marked are not suitable where onset of action is slow. Thus chewable tablet achieve high bioavailability and rapid onset of action. Particularly one that disintegrates and dissolves or disperses in saliva and administered without need of water. It has unacceptable taste and present study to formulate the chewable tablet with taste masked. My attempt was made in the present work to formulate and evaluate chewable tablet of sildenafil citrate.

"Generally, in man, oral administration of the phospho diesterase inhibitors is the preferred route, being the most convenient and avoiding the disadvantages associated with intra cutaneous administration. Phospho diesterase inhibitors include drugs such as Sildenafil Citrate and they are available in the market in form of a film-coated tablet, wherein, film-coating has to dissolve and tablet has to disintegrate into granules and further the drug has to release for dissolution in acidic media of stomach. Normal mouth dispersible tablets release the drug for absorption in oral cavity. Further Sildenafil is very bitter to taste PDE inhibitors. Hence formulation development is very critical. Effectiveness of any phospho diesterase inhibitor formulation will depend upon initial complexation to the extent necessary to bypass taste buds without detection with the ability to subsequently release the drug from the

complex after pH adjustment in digestive tract. Dispersible tablets are the formulations that elude the process of disintegration that occurs with conventional formulation, dispersible tablets are formulated to make the drug product bio-available at a faster rate for immediate action.

In the present study of sildenafil citrate was designed, for the following reasons.

- Sildenafil citrate pure drugs are bitter taste. Ph-modification method. Higher dosage forms are administered into the chewable tablet form. Prevent from into the first pass metabolism. High solubility and high permeability.
- Sildenafil citrate is used in the treatment of erectile dysfunction and also used into the pulmonary hypertension. Sildenafil citrate has a vasodilator properties resulting in mild and transient decrease in the blood pressure. Quick on set of action.

MORINGA OLEIFERA:

Moringa oleifera is a small genus of quick growing tree distributed in India. The stem of the tree exudes a gum which is initially white in colour but changes to reddish brown or brownish black on exposure to sunlight. It is sparingly soluble in water but swells in contact with water giving a highly viscous solution. Moringa oleifera gum Binder and release retardant in tablet. Binders are agents used to cohesive quality to the material during the production of the tablet. They import cohesiveness of the tablet formulation. Which ensures that the tablet remain intact after compression as well as improving the free flowing quality. Binders have been used as the solution in the formulation and the method of preparation. The choice of a particular binding agent depends on the binding force required to form the granules and compatability with the other ingredients particularly the active drug. It is

polyuronide consisting of arabinose, galactose and glucoronic acid in the proportion of 10:7:2, rhamnose is present in traces. It was observed that drug release increased with increasing proportions of the excipient and decreased proportion of the gum. Gum was also studied for its disintegrating property. Different batches of tablets were formulated varying them by quantity of the gum. It was observed that wetting time decreased with the increase in concentration of gum in formulation.

PLAN OF WORK

3.2 PLAN OF WORK

The present work was carried out to formulate development and evaluate the chewable tablet by taste masking of sildenafil citrate.

- Chewable tablet prepared by direct compression method.
- Mannitol is widely used as excipients in chewable tablet for its non-hygroscopic nature for moisture sensitive drug.
- Using artificial sweeteners may provide a satisfactory alternative.
- Taste masking method using dried calcium carbonate different concentration ratio. Taste masking method was performed by Ph-Modification method.
- Adjustment of pH Values: Many drugs are less soluble at pH different from the pH value of the mouth, which is around 5.9. Solubilization inhibitor, such as sodium carbonate, sodium bicarbonate, sodium hydroxide, or calcium carbonate, was added to increase the pH when granules' including a sildenafil citrate-dissolved in aqueous medium, the bitter taste of the drug was successfully masked by a sweetener alone.
- Performing in Drug-Excipients compatibility studies by IR studies.

3.2.1. Physic-chemical evaluation of the chewable tablet.

- Preformulation studies
- Evaluation of blend
- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner's ratio

3.2.2. Evaluation of chewable tablet

- Weight variation.
- Hardness
- Friability
- Thickness
- Drug content
- disintegration time
- Wetting time

CHAPTER 4
DRUG AND EXCIPIENT PROFILE

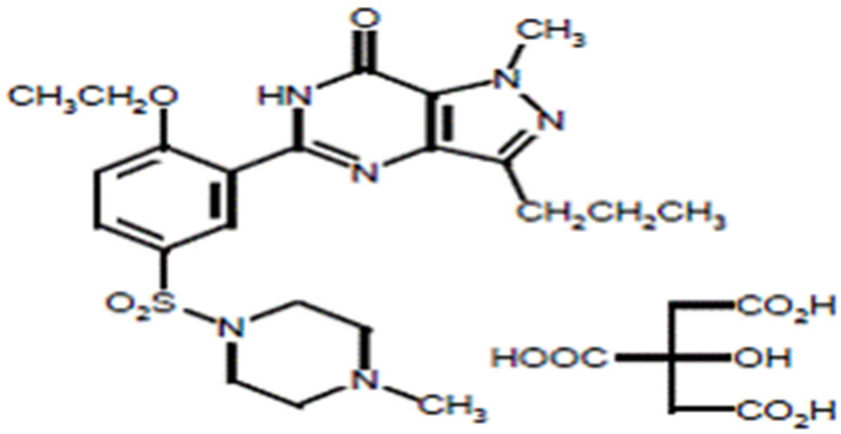
4. DRUG AND EXCIPIENTS PROFILE

4.1 Drug profile.[27]

4.1.1. Identification:

4.1.1.1. Drug name: sildenafil citrate

4.1.1.2. Structure:



4.1.1.3. Chemical formula : $C_{28}H_{38}N_6O_{11}S$

4.1.1.4. Molecular weight : 666.703g/mol

4.1.1.5. Melting point : 189-190 °C

4.1.1.6. Dose : 25mg, 50mg, 100mg

4.1.1.7. Type : Small molecule

4.1.1.8 .Category : Erectile dysfunction, pulmonary hypertension

4.1.1.9. Description : white to almost white, crystalline powder. It aqueous solubility is equivalent to 2.6mg sildenafil per ML at 25^0c.

4.1.1.10. Route of administration: oral route, Transdermal gel

4.1.1.11. BCS classification : Class-I

4.1.2. Storage: Store below 30^0c

4.1.3.Mechanism of action: Sildenafil citrate inhibits the cGMP-specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum located around the penis. penile erection during the period of sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus smooth muscle. This response has mediated the synthesis of cGMP in smooth muscle cells .cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE %) by sildenafil enhances erectile function by increasing the amount of cGMP>90%absorbed with ~40% reaching circulation into the following first pass metabolism.

4.1.4. Taxonomy:

4.1.4.1. Kingdom **:** Organic

4.1.4.2. Classes **:** Phosphodiesterase type-5

4.1.5. Pharmacokinetic profile:-

4.1.5.1. Absorption: - >90% absorbed with ~40% reaching systemic circulation unchanged following first pass metabolism.

4.1.5.2. Protein binding: 96% Sildenafil appears to be completely metabolized in the liver to 16 metabolites. Its metabolism is mediated mainly by cytochrome P450 microsomal isozymes 3A4 (major route) and 2C9 (minor route). The major circulating metabolite, *N*-demethylated metabolite, has PDE selectivity similar to the parent drug and ~50% of it's *in vitro* potency. The *N*-demethylated metabolite is further metabolized to an N-dealkylated *N, N*-de-ethylated metabolite. Sildenafil also undergoes *N*-dealkylation followed by *N*-demethylation of the piperazine ring.

4.1.5.3. Half life **: -** 4hours

4.1.5.4. Metabolism **: -** Hepatic.

4.1.5.5. Excretion **: -** lesser extent in the urine (approximately 13% of the administered oral dose).

4.1.5.6. Adverse effect: - A headache, urinary tract infection, diarrhea, Cardiac death, myocardial infection.

4.1.5.7. Therapeutic use: - it's used in the treatment of erectile dysfunction, and pulmonary hypertension.

4.2. Excipient Profile.

4.2.1. Calcium carbonate[28]

4.2.1.1. Non-Proprietary Name:-

BP	:	calcium carbonates (1:1)
JP	:	carbonic acid calcium salt (1:1)
PHEUR	:	calcium carbonate
USP	:	calcium carbonate

4.2.1.2. Synonyms:-

Cali carbons: calcium carbonates (1:1); precipitated carbonate lime; precipitated chalk;

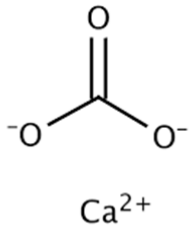
4.2.1.3. Chemical name:-

Carbonic acid: calcium salt;

4.2.1.4. Empirical formula and molecular weight:-

$Caco_3$, 100.9

4.2.1.5. Structure Formula:-



4.2.1.6. Functional category:

Buffering agent, coating agent, opacifiers, tablet binders, tablet diluents, therapeutic agents.

4.2.1.7. Application in pharmaceutical formulation or technology:-

Mainly used solid-dosage forms of diluents. Dissolution aid in dispersible tablets.$caco_3$ bulking agents. Tablets sugar coating on opacifier in film coating tablets.

4.2.1.8. Typical properties:-

Density bulk	:	0.8kg/cm^3
Floability	:	cohesive
Hardness	:	3.0kg/cm^3
Refractive index	:	1.59

4.2.1.9. Stability and storage conditions:-

Calcium carbonate is stable and should be stored in well-closed containers.

4.2.2. Polyvinyl Pyrolidine k.30[29]

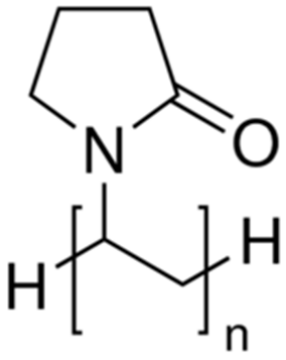
4.2.2.1. Synonym: - PVP

4.2.2.2. Chemical Name:

POLYVINYL PYROLIDINE K 30

4.2.2.3. Molecular formula: - (-CH ($NCH_2CH_2CH_2CO$) CH2-) n

4.2.2.4. Structure:-



4.2.2.5. Functional category:-

Clarifying agents; stabilizers

4.2.2.6. Application:-

Clarifying agents; stabilizers; thickeners agent; tablet fillers; dispersants; PVP of molecular weight 360,000 are often used as the clarifying agent of beer, vinegar, and grapewine. Used as the fixing liquid for gas chromatography. It is used as a colloidal stabilizer and clarifying agent for beer clarification. Apply proper amount according the demands of production. It can be used for pharmacy, aquaculture, and livestock disinfectant for the sterilization of the skin and mucous.[30]

4.2.2.7 Storage:-

Keeped in dry place at the room temperature.

4.2.3. Crosspovidone[31]

4.2.3.1. Non-Proprietary Name:

BP : crospovidone

PHEUR : crospovidone

USP-NF : crospovidone

4.2.3.2. Synonms:-

Crospovidone;crosphopham;crosslinkedpovidone;polyvinylpyrolidone; pvpp; 1-vinyl-2-pyrrolidinone homopolymer.

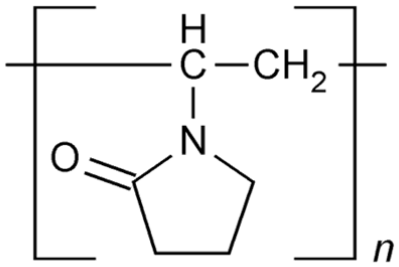
4.2.3.3. Chemical Name:-

1-ethenyl-2-pyrolidinone homopolymer.

4.2.3.4. Empirical formula and Molecular Weight:-

$(C_6H_9N)>1000000$

4.2.3.5. Structure:-



4.2.3.6. Functional category:-

Tablet disintegrant.

4.2.3.7. Stability and storage conditions:-

Povidone darkens to some extent on heating at 150^0c, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130^0c,steam sterilization of an aqueous solution dose not alter its properties. Aqueous solution is susceptible to mold growth and consequently require the addition of suitable preservatives. Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.[28]

4.2.3.8. Application in pharmaceuticals:-

Since crospovidone is water insoluble tablet disintegrant and dissolution agent used 2-5%concentration tablet prepared by direct compression or wet and dry – granulation method. Crospovidone can be used enhance the solubility of the poorly soluble drug.

4.2.3.9. Description:-

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidone with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidone are manufactured by drum drying and occur as plates.

4.2.3.10. Incompatibilities:-

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. Thimerosal, may be adversely affected by the formation of complexes with povidone.

4.2.4. Cross carmellose sodium

4.2.4.1. Nonproprietary Name: - Croscarmellose sodium

4.2.4.2. Synonyms:-

Ac-di-sol; carmellosum natricum conexum; Crosslinked carboxymethylcellulose sodium; Explocel: modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose;

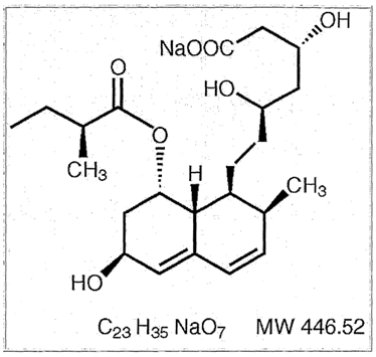
4.2.4.3. Chemical Name:-

Cellulose, carboxymethyl ether.

4.2.4.4. Molecular Weight:-

90000-700000

4.2.4.5. Structural Formula:-



4.2.4.6. Functional Category:-

Tablet and capsule disintegrant.

4.2.4.7. Description:-

Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

4.2.4.8. Solubility:-

Insoluble in water, although Croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol, and toluene[32]

4.2.4.9. Stability and Storage Conditions:-

Croscarmellose sodium is a stable though the hygroscopic material. A model tablet formulation prepared by direct compression, with Croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 3000C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

4.2.4.10. Incompatibilities:-

The efficacy of disintegrant such as Croscarmellose sodium may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose Sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

4.2.4.11. Applications:-

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, Croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the Croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra- granularly) so that the wicking and swelling ability of the disintegrant are best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3%w/w in tablet prepared by wet granulation process.

4.2.4.12. Related Substances: -

Carboxy methyl cellulose calcium: Carboxy methyl cellulose sodium

4.2.5. Mannitol[33]

4.2.5.1. Nonproprietary Names:-

- BP : Mannitol
- JP : D-Mannitol
- PHEUR: Mannitolum
- USP :Mannitol

4.2.5.2. Synonyms:-

Cordycepic acid, E421, manna sugar, D-mannite, mannite, Mannogem, pearlitol.

4.2.5.3. Chemical Names:-

D-Mannitol

4.2.5.4. Empirical formula and Molecular Weight:-

$C_6H_{14}O_6$. 182.17

4.2.5.5. Functional Category:-

Diluent, diluents for lyophilized preparations, sweetening agent, tablet and capsule diluents, tonicity agent.

4.2.5.6. Applications in Pharmaceuticals Formulation or Technology:-

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10 – 90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glycerly trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'. In lyophilized preparations, mannitol (20-90% w/w) has been included as a carries to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use[34].

Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v).It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carries in dry powder inhalers. It is also used as diluents in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent.

Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agents for kidney function,as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure .given orally, mannitol is not absorbed significantly from the GI tract, but in large doses it can cause osmotic diarrhea.

4.2.5.7. Description:-

Mannitol is D-Mannitol.it is a hexahydric alcohol related mannose and is isomeric with sorbitol.Mannitol occurs as a white, odourless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

4.2.5.8. Stability and storage conditions:-

Mannitol is stable in the dry state and in aqueous .solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold, dilute acids, alkali, or by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo maillaard reaction. The bulk material should be stored in a well-closed container in a cool, dry place.

4.2.5.9. Incompatibilities:-

Mannitol solutions, 20%w/v or stronger, may be salted out potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25%w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/ml and 30 mg/ml concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatibilities with xylitol infusion and may from complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation. Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.

4.2.6. Aspartame[35]

4.2.6.1 Non-Proprietary Name:-

BP: aspartame

PHEUR: aspartame

USP-NF: aspartame

4.2.6.2. **Synonyms:-**

(3S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl] amino]-4-

Oxobutanoic acid; 3-amino-N-(a-carboxyphenethyl) succinamic

Acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)-

Succinamic acid; APM; aspartame; aspartyl phenyl amine methyl

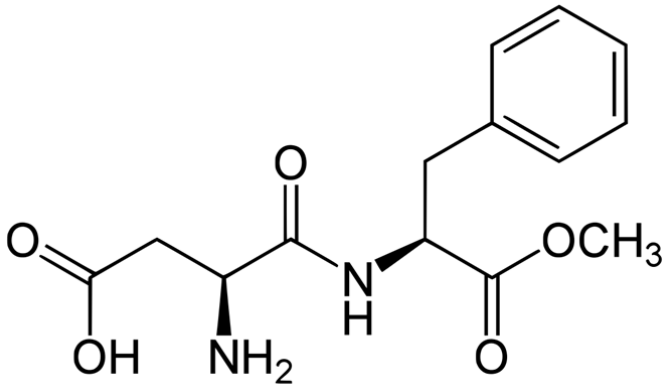
4.2.6.3. Chemical name:-

N-L-a-Aspartyl-L-phenylalanine 1-methyl ester.

4.2.6.4. Empirical formula and molecular weight:-

$C_{14}H_{18}N_2O_5$ 294.30

4.2.6.5. Structure:-



4.2.6.6. Functional category:

Sweetening agents.

4.2.6.7. Application:

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,(1,2) powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides minimal nutritive agents[36].

4.2.6.8. Description:

Aspartame occurs as an off white, almost odorless crystalline Powder with an intensely sweet taste.

Density (true) 1.347 g/cm3

Effective angle of internal friction 43.08(3)

Melting point 246–2478C

4.2.6.9. Stability and Storage Conditions:

Aspartame is stable in dry conditions. In the presence of moisture, Hydrolysis occurs to form the degradation products L -aspartyl-L phenylalanine And 3-benzyl-6-carboxymethyl-2,5-diketopiperazine with a resulting loss of sweetness. A third-degradation product is also known, b-L-asparty phenylalanine methyl ester. For the stability profile at 258C in aqueous buffers.

4.2.7. Aerosil

4.2.7.1. Nonproprietary Names:-

BP: Colloidal Anhydrous Silica

JP: Light Anhydrous Silicic Acid

PhEur: Silica, Colloidal Anhydrous

USP-NF: Colloidal Silicon Dioxide

4.2.7.2. Synonyms:-

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica;

Fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica

Colloidalis anhydrica.

4.2.7.3. Chemical name:-

Silica

4.2.7.4. Empirical Formula and Molecular weight:-

Sio_2 60.08

4.2.7.5. Functional Category:-

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

4.2.7.6. Application in pharmaceutical Formulation or Technology:-

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling. Colloidal silicon dioxide is also used to stabilize emulsions andas a thixotropic thickening and suspending agent in gelsandsemisolid preparations.With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxidethan nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity; In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.[37]

Aerosols-concentration 0.5-2.0

Emulsion stabilizer-1.0-5.0

Glidant-0.1-0.5

Suspending agent-2.0-10.0

4.2.7.7. Description:-

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

4.2.7.8. Stability and Storage Conditions:-

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container.[38]

4.2.7.9. Incompatibilities:-

Incompatible with diethylstilbestrol preparations

4.2.8. Talc

4.2.8.1. Synonyms:-

Altalc, E553b, hydrous magnesium calcium silicate, hydrous magnesium silicate, Luzenac phrama, magnesium hydrogen metasilicate, Magsil Osmanthus, Magsil star, powdered talc, purified French chalk,Purtalc, soapstone, superior.

4.2.8.2. Empirical Formula and molecular Weight:-

Talc is purified, hydrated, magnesium silicate, approximating to the formula Mg_6 $(Si_2O_5)4(OH)4$. It may contain small, variable amounts of aluminum silicate and iron. Molecular weight is 260.8617

4.2.8.3. Structural Formula:-

$Mg_3Si_4O_{10}$ $(OH)_2$

4.2.8.4. Functional Category:-

Anti caking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant.

4.2.8.5. Applications in Pharmaceutical Formulation or Technology:-

Talc was once widely used in oral solid dosage formulation as a lubricant and diluents, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations, in a novel powder coating for extended-release pellets, and as an adsorbent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is a natural material; it may therefore frequently contain microorganisms and should be sterilized when used as a dusting powder.[39]

- Dusting powder –concentration (90.0-99.0%)
- Glidant and tablet lubricant-1.0-10.0
- Tablet and capsule diluents-5.0-30.0

4.2.8.6. Description:-

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

4.2.8.7. Incompatibilities:-

Incompatible with quaternary ammonium compounds.

4.2.9. Starch

4.2.9.1. Non-proprietary Name:-

BP: Maize starch

JP: Corn Starch

PhEur: Maize Starch

4.2.9.2. Synonyms:-

Amido; amidon; amilo; amylum; PharmGel; Eurylon; fecule; Hylon; maydis amylum; Melojel; Meritena; oryzae amylum;

4.2.9.3. Empirical formula and molecular weight:-

$(C_6H_{10}O_6)_n$where n = 300–1000.

4.2.9.4. Functional category:-

Tablet and capsule diluent; tablet and capsule disintegrant; tabletbinder; thickening agent.

4.2.9.5. Application in pharmaceuticals

Starch is a versatile excipient used primarily in oral solid-dosageformulations where it is utilized as a binder, diluent, anddisintegrant.As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations.Starch is also used in dry-filled capsule formulations forvolume adjustment of the fill matrix,and to improve powder flow, especially when using dried starches. Starch quantities of 3–10% w/w can act as an antiadherent and lubricant in tableting and capsule filling. In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on thestarch type) as a binder for wet granulation. The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate. Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w.

4.2.9.6. Description:-

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

4.2.9.7. Stability conditions:-

Dry starch is stable if protected from high humidity. Starch is Considered to be chemically and microbiologically inert under both amylose and amylopectin have been evaluated as safe and without limitation for daily intake. Contamination of surgical wounds with the starch glove powder used by surgeons has resulted in the development of granulomatouslesions.

4.2.10.8. Incompatibility:-

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

4.2.10.9. Safety:-

Starch is an edible food substance, considered a food ingredient and not a food additive. It is regarded as an essentially nontoxic and nonirritant material. Starch is therefore widely used as an excipient in pharmaceutical formulations.

4.2.10. Citric acid monohydrate[40]

4.2.10.1. Non-Proprietary Name:-

BP : citric acid mono hydrate.

JP : citric acid hydrate.

PHEUR: citric acid mono hydrate.

USP : citric acid mono hydrate.

4.2.10.2. SYNONMS:-

Acidum citricum monohydricum; 1, 2, 3 tri carboxylic acid.

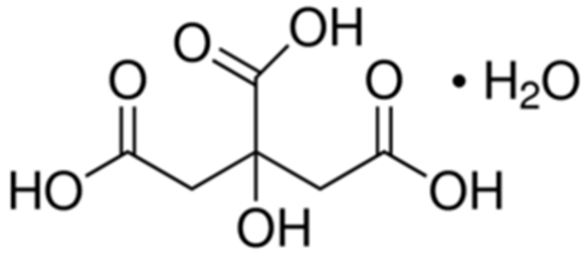
4.2.10.3. Chemical name:-

2-hydroxy- 1, 2, 3 propanetric carboxylic acid mono hydrate

4.2.10.4. Empirical formula and molecular weight:-

$C_6H_8O_7.H_2O$ 210.14

4.2.10.5. Structural formula:-



4.2.10.6. Functional category:-

Acidifying agent; antioxidants; buffering agents; chelating agents; flavoring agents.

4.2.10.7. Application:-

Widely used in pharmaceutical formulations and food products; primarily adjust the PH of the solutions. It also used in the experimental for the tablets PH adjust and also using tablets material in enteric coating tablets in the colon specific drug delivery systems. Citric acid used in the flavors' enhancers for it acidic taste.

4.2.10.8. Stability and storage conditions:-

Citric acid mono hydrate is a loss of water for crystallization in dry air. When heated at about 40^0c.it slightly deliquescent in moist air .dilute aqueous solution of the citric acid may be ferment on standing.[41]

4.2.10.9. Description:-

Citric acid monohydrate is translucent crystals, or white crystalline, efflorescent powders. It is an odorless and strong acidic taste.

4.2.10.10. Typical properties: -

Density: 1.542g/cm^3

Hygroscopicity: AT relative humidity at 25^0c.the bulk monohydrate and anhydrous materials at the store at air tight containers and store in cool place.

4.2.10.11. Methods of manufacture:-

Citric acid occurs naturally in a number of plant species and may be extracted from lemon juice, which contains 5–8% citric acid Pineapple waste. Anhydrous citric acid may also be produce industrially by mycological fermentation of crude sugar solutions Such as molasses, using strains of aspergillums Niger. Citric acid is purified by recrystallization; the anhydrous form is obtained from a hot concentrated aqueous solution and the monohydrate from a Cold concentrated aqueous solution.

4.2.11. Magnesium stearate:-

4.2.11.1. Synonyms:-

Magnesium octadecanoate; Octadecanoic acid, magnesium Salt; Stearic acid, magnesium salt.

4.2.11.2. Chemical Name:-

Octadecanoic acid magnesium salt.

4.2.11.3. Molecular Formula:-

$C_{36}H_{18}N_{25}0_5$

4.2.11.4. Molecular weight:-

591.34

4.2.11.5. Functional category:-

Tablet and capsule lubricant.

4.2.11.6. Application in pharmaceutical Formulation or Technology:-

It is widely used in cosmetics, food and pharmaceutical Formulation. It is primarily used as a lubricant in capsule in barrier creams. And tablet manufacture at concentrations between 0.25% and 5.0% w/w.

4.2.11.7. Stability and Storage:-

It is stable and should be stored in a well-closed container In a cool, dry place.

4.2.11.8. Incompatibilities:-

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. It cannot be used in products containing aspirin, some vitamins, and most alkaloid salts.

4.2.11.9. Safety:-

Nontoxic following oral administration. However, oral Consumption of large quantities may produce a laxative Effect or mucosal irritation.[42]

CHAPTER 5
MATERIALS AND METHODS

5.1 MATERIALS AND METHODS

The Materials used in the present work are as follows.

S NO	Materials	Name of the supplier
1.	Sildenafil citrate	Chandra labs, hyd
2.	Dried calcium carbonate	MYL CHEM MUMBAI
3.	Oyster Calcium Carbonate	Chandra labs, hyd
4.	PvP k30	MYL CHEM Mumbai
5.	Crospovidone	MYL CHEM Mumbai
6.	Croscarmellose sodium	MYL CHEM Mumbai
7.	Mannitol	S.D Fine Chem. LTD Mumbai
8.	Aspartame	S.D Fine Chem. LTD Mumbai
9.	Lemon flavor	MYL CHEM Mumbai
10.	Peppermint flavor	MYL CHEM Mumbai
11.	Sunset yellow lake	MYL CHEM Mumbai
12.	Aerosil	S.D Fine Chem. LTD Mumbai
13.	Talc	MYL CHEM MUMBAI
14.	Magnesium stearate	Chandra, labs hyd
15.	Citric acid monohydrate	S.D FINE CHEM.LTD.

5.2 MATERIALS AND METHOD

The Materials used in the present work are as follows.

S. NO.	Materials	Name of the supplier
1.	Sildenafil citrate	Chandra labs, hyd
2.	Dried Calcium carbonate	Chandra labs, hyd
3.	Moringa gum	Local Nursery
4.	Aerosil	MYL CHEM Mumbai
5.	Starch	MYL CHEM Mumbai
6.	Mannitol	S.D Fine Chem. LTD Mumbai
7.	Citric acid monohydrate	S.D Fine Chem. LTD Mumbai
8.	Lemon flavor	MYL CHEM Mumbai
9.	Peppermint flavor	MYL CHEM Mumbai
10.	Sunset yellow lake	MYL CHEM Mumbai
11.	Talc	S.D Fine Chem. LTD Mumbai
12.	Magnesium strearate	MYL CHEM MUMBAI

5.3. Equipment

The equipment used in the present work are as follows

S.no	Instruments	Source
1	Electronic balance	Shimadzu japan
2	UV/Visible Spectrophotometer	Corporation-BL-220H
3	FTIR spectrophotometer	Corporation Japan
4	Dissolution apparatus	Shimadzu japan
5	Hot Air Oven	Biotech India.
6	Compression machine	Cadmach machinery

5.1.1. METHODOLOGY

5.1.1.1. Preformulation studies

5.1.1.2. Construction of standard graph of sildenafil citrate in 0.01N HCL.

5.1.1.3. Preparation of 0.01N HCL.

1. Take 8.5ml of Conc.HCl in distilled water and makeup to 10000ml with distilled Water to get 0.01N HCl[43].
2. **Construction of standard graph of sildenafil citrate in 0.01n hcl.**
3. **Preparation of stock solution.**

a. The accurately weighed amount of 30 mg was transferred into a 100ml volumetric flask. And the volume was made up to 50 mL with 0.01N HCl.

4. **Preparation of working standard solution.**

a. From this stock solution, 2.5,4,5,6,7.5 was taken and diluted to 50 mL with 0.01N HCl which has given the solution having the concentration of 100 mcg/mL

5. **Preparation of serial dilutions for standard calibration curve.**

Necessary dilutions were made by using this second solution to give the different concentrations of sildenafil citrate (2.5,4,5,6,7.5 mcg/mL) solutions.

The absorbance of above solutions was recorded at λ_{max} (290 nm) of the drug using double beam UV-Visible spectrophotometer. A standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

5.2.1. Drug – excipient compatibility study

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-500 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powdered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15MM diameter and pellet of suitable intensity by hydraulic press. The

infrared spectrum of sildenafil citrate was recorded by using FT-IR spectroscopy and observed for characteristic peak of drug, and undisturbed drug structure of the drug, which indicates there was no drug.[44]

5.2.2. Formulation of chewable tablet (direct compression method)

The chewable tablets containing 100mg sildenafil citrate were prepared with a total tablet weight of 700mg. All the formulations were prepared by direct compression.[45]

Procedure

1. Sildenafil citrate and all other ingredients were individually passed through a sieve no.40.

   All the ingredients were mixed thoroughly by triturating up to 15minties.
2. The powder mixture was lubricated with Magnesium stearate. The tablets were prepared by using direct compression method according to the formulation table.
3. Then the blend was compressed using 13MM Flat beveled edged scored on one side

Table No: 1 Composition of different formulations for chewable tablet by Direct Compression Method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sildenafil citrate	143	143	143	143	143	143	143	143	143
Calcium carbonate(dried)	70	140	210	280	350	--	350	350	350
Calcium carbonate(oyster shell)	--	--	--	--	--	350	--	--	--
PVP k.30	21	21	21	21	21	21	21	21	21
Purified water	--	--	--	--	--	--	--	--	--
Crospovidone	--	15	25	30	35	35	--	35	--
Cros carmellose sodium	--	15	25	30	35	35	35	--	--
Micro Crystalline Cellulsoe	--	---	---	---	---	---	---	---	35
Aspartame	16	16	16	16	16	16	16	16	16
Lemon flavor	7	7	7	7	7	7	7	7	7
Peppermint flavor	4	4	4	4	4	4	4	4	4
Sunset yellow lake	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Mannitol	404	304	214	134	54	54	89	89	89
Aerosil	7	7	7	7	7	7	7	7	7
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	7	7	7	7	7	7	7	7	7
Citric acid monohydrate	14	14	14	14	14	14	14	14	14
Avg.weight total	**700mg**	**700mg**	**700mg**	**700mg**	**700mg**	**700mg**	**700mg**	**700mg**	**700mg**

5.2.3. Chewable tablet (direct compression method)

After the batch was optimized and compared with (F5) and (F6). (F6) was more compatible with best (F5). (F6) formulation produce tastes masked but grittiness formed. The optimized batch in both was compressed by using same ingredients but different calcium carbonate (oyster shell).F7-F9 using super disintegrants like croscarmellosesodium, crospovidone.

5.2.4. Formulation of chewable tablet (wet granulation method)

The tablets containing 100mg sildenafil citrate were prepared with a total tablet weight of 700mg. All the formulations were prepared by wet granulation method.[43]

5.3.1. Isolation of moringa oleifera gum

The gum was collected from trees (Injured site). It was dried, ground and passed through sieve no 80. Dried gum (10g) was stirred in distilled water (250ml) for 6-8 hours at room temperature. The supernatant was obtained by centrifugation. The residue was washed with water and the washings were added to supernatant. The procedure was repeated four times. Finally the supernatant was made up to 500 ml and the treated with twice the volume of acetone by continuous stirring. The precipitated material was washed with distilled water and dried at 50-60ºC under vacuum.

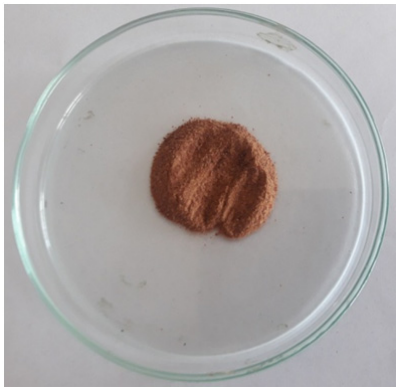


Figure no.5 Moringa gum

5.3.2. Formulation of tablet

The tablets of sildenafil citrate were prepared by wet granulation method using *Moringa Oleifera* gum, dried calcium carbonate as taste masking agent, Starch as binder, Purified talc and Magnesium Stearate as lubricant and Aerosil as glidant .citric acid monohydrate as adjust Ph of the solutions. The drug and other ingredients with half quantity of disintegrant were mixed together, sufficient quantity of starch paste was added to form coherent mass. The wet mass was granulated using sieve No. 40 and the granules formed were dried into hot Air oven at 40ºC for 20 minutes and regranulated using sieve no 20. The granules were blended with remaining quantity of the disintegrant (extra granular disintegrant), purified talc, aerosil and compressed into 13MM Flat beveled edged scored on one side (Compression machine, Ahmedabad, India).

Table No: 2 Composition of different formulations for wet granulation method

Sr. No.	Ingredients	Quantity in mg		
		F10	F11	F12
1.	Sildenafil citrate	143	143	143
2.	Dried calcium carbonate	350	350	350
3.	Moringa gum	4	6	8
4.	Starch	15	15	15
5.	Citric acid monohydrate	14	14	14
6.	Aerosil	4	4	4
7.	Lemon flavor	7	7	7
8.	Peppermint flavor	4	4	4
9.	Sunset yellow lake	3.5	3.5	3.5
10.	Mannitol	148.5	146.5	144.5
11.	Talc	4	4	4
12.	Magnesium strearate	3	3	3
	Avg.weight total	700mg	700mg	700mg

5.4.1. EVALUATION OF PRECOMPRESSION BLEND[46]

- **Flow Properties:**
- **The angle of Repose:**

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

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

Where,

h = height of a pile (2 cm)

r = radius of pile base.

5.4.2. Procedure

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn with a pencil on the graph paper.
- The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

5.4.3. Bulk density

Bulk density is the ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus into the cup.

$$\text{Bulk density} = M / V_0$$

Where M= mass of the powder;

The V_0=bulk volume of the powder.

Limits:

It has been stated that the bulk density values having less than 1.2 g/cm^3 indicates good Packing and values greater than 1.5 g/cm^3 indicates poor Packing.

5.4.4. Tapped density

A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times than reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading was taken until little further volume changes are observed.

Tap density = M / Vr

Where M = mass of the powder,

Vr = final tapping volume of the powder.

5.4.5. Compressibility index and Hauser's ratio

The compressibility index and Hausner's ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

Hauser's ratio = tapped density / bulk density

Flow properties and corresponding Angle of repose, Compressibility index and Hauser's ratio:

Table No: 3 ACCEPTANCE CRITERIA OF FLOW PROPERTIES

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner'sratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	> 66	>38	>1.6

5.5.1. Evaluation of tablets

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and in-vitro dissolution characters.

5.5.2. Hardness

The hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.[47]

5.5.3. Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depending on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Callipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition, the thickness must be controlled to facilitate packaging.

5.5.4. Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. It is usually measured by the use of the Roche friability.[48]

Method

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After that rotate the drum at 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

5.5.5. Drug content

Twenty tablets were selected randomly from each batch, weighed and made into a fine powder. The quantity of powder equivalent to 30mg of sildenafil citrate was dissolved in 100ml of 0.01NHCL buffer and the resultant solution was filtered and filtrate obtained was suitably diluted with the Ph 3 0.01NHcl.sildenafil citrate content was determined spectrometrically by measuring the absorbance at 290 nm using Shimadzu UV1601 Double beam spectrophotometer. The test was carried out in triplicate for all the formulations and the drug content was calculated and reported. [49]

5.5.6. Wetting time:

Wetting time is closely related to the inner structure of the tablet and to the hydrophilicity of the excipients. According to the following equation proposed by washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by hydrophilicity of the powder.

$$Di/dt = r\gamma\cos\theta / (4\acute{\eta}l)$$

Where I is the length of penetration, r is the capillary radius is the surface tension, $\acute{\eta}$ is the liquid viscosity, t is the time, and θ is the time, and θ is the contact angle. It is obvious that pore size becomes smaller and wetting time increase with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is important step for disintegration process to place. A place tissues paper folded double was placed in Petri dish .(internal diameter is 6.5cm)containing 6ml of water .the tablet was placed on the paper ,and the time for complete wetting of the tablet was measured in the seconds .the method was slightly modified by maintaining water at 37^0C.wetting time was evaluated .[50]

5.5.7. Disintegration time:

The disintegration test is carried out in apparatus containing a basket rack assembly with six glass tubes of 7.75cm in length and 2.15 mm in diameter, the bottom of which Consists of a#10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900ml water which is maintained at 37±2°C. Six tablets were placed in each of the tubes and the time required for completer passage of tablet fragments through the mesh (#10) was considered as the disintegration time of the tablet.[49]

5.5.8. Dissolution studies

5.5.9. In vitro dissolution studies for chewable tablet

In vitro, drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for an hour, at 100 rpm, 0.01N HCl adjust (PH-3) was used as a dissolution medium. 5ml of the sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug-free dissolution fluid. The samples withdrawn were filtered through a 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 290nm.

5.6.1. STABILITY STUDIES OF THE TABLET

Stability of a formulation can be defined as the time from the date of manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Formulation and the development of a pharmaceutical product are not complete without proper stability analysis, carried out on it to assess their physical and chemical stability and the safety. The purpose of stability testing is to provide

evidence on how the quality of a drug substance of drug product varies with time. Under the influence of a variety of environmental factors such as temperature, humidity, and light enabling recommended storage conditions, re-tests periods and shelf- lives.

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of the accelerated stability studies are adapted.

The international conference on harmonization (ICH) guidelines titled "Stability Testing of New Drug Substances and Product" describes the stability test requirements for drug registrations application in the European Union, Japan, and the USA. ICH specifies the length of study and storage Conditions.

Long-Term testing: 25±2°C/60%±5% RH for 12 months.

Accelerated Testing: 40±2°C/75%±5% RH for 3 months.

Stability studies for the present work carried out at 40°C/75%RH for the selected formulation (F5) for 3 months.

Method

The selective formulations stored at 40°C/75%RH for 3 months and evaluated for their physical appearance and drug content at a specified interval of time. and also performed were in vitro dissolution studies.

CHAPTER 6
RESULT AND DISSCUSSION

6.1. Result and Discussion

6.1.1. Standard calibration curve of sildenafil citrate

6.1.2. Concentration and absorbance of sildenafil citrate in 0.01N Hcl

S.No	Concentration[µg/ml]	Absorbance at 290nm
1.	0	0
2.	50	0.317
3.	80	0.419
4.	100	0.599
5.	120	0.718
6.	150	0.901

Figure no.6.1. Standard calibration curve of Sildenafil citrate

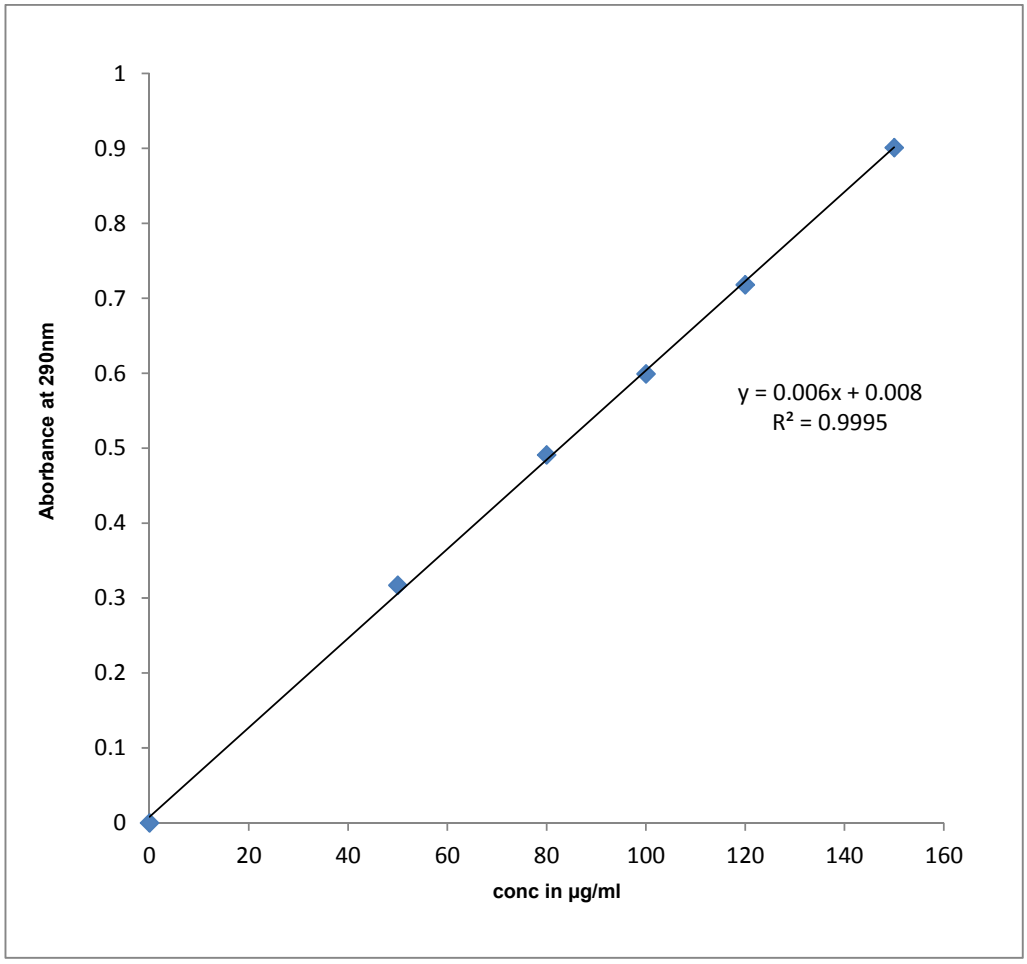


Figure no .6.2. I R Spectra of Sildenafil citrate pure drug

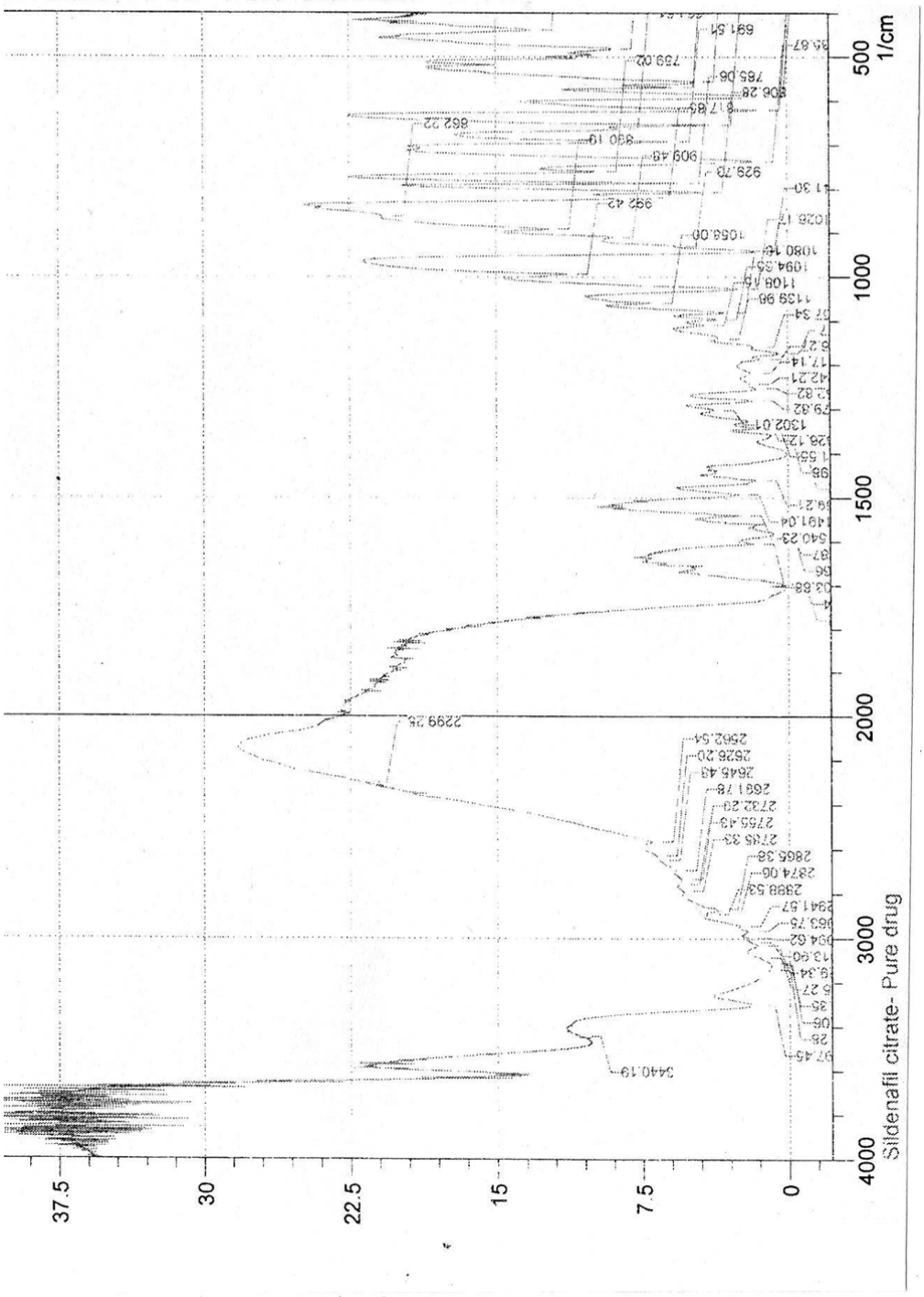


Figure no .6.3. IR Spectra of Sildenafil citrate+ Dried calcium carbonate

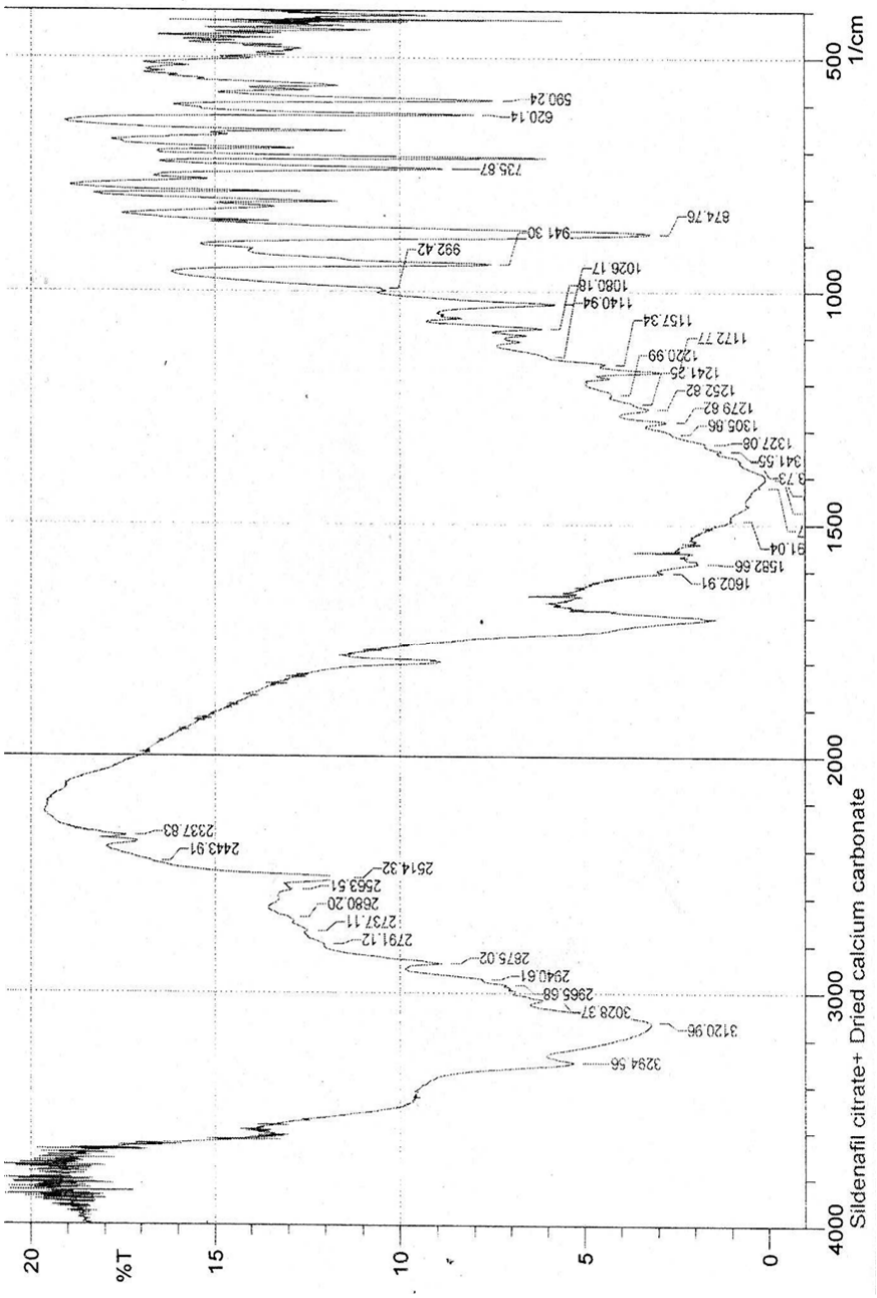


Figure no.6.4.IR spectra of sildenafil citrate + calcium carbonate (oyster shell)

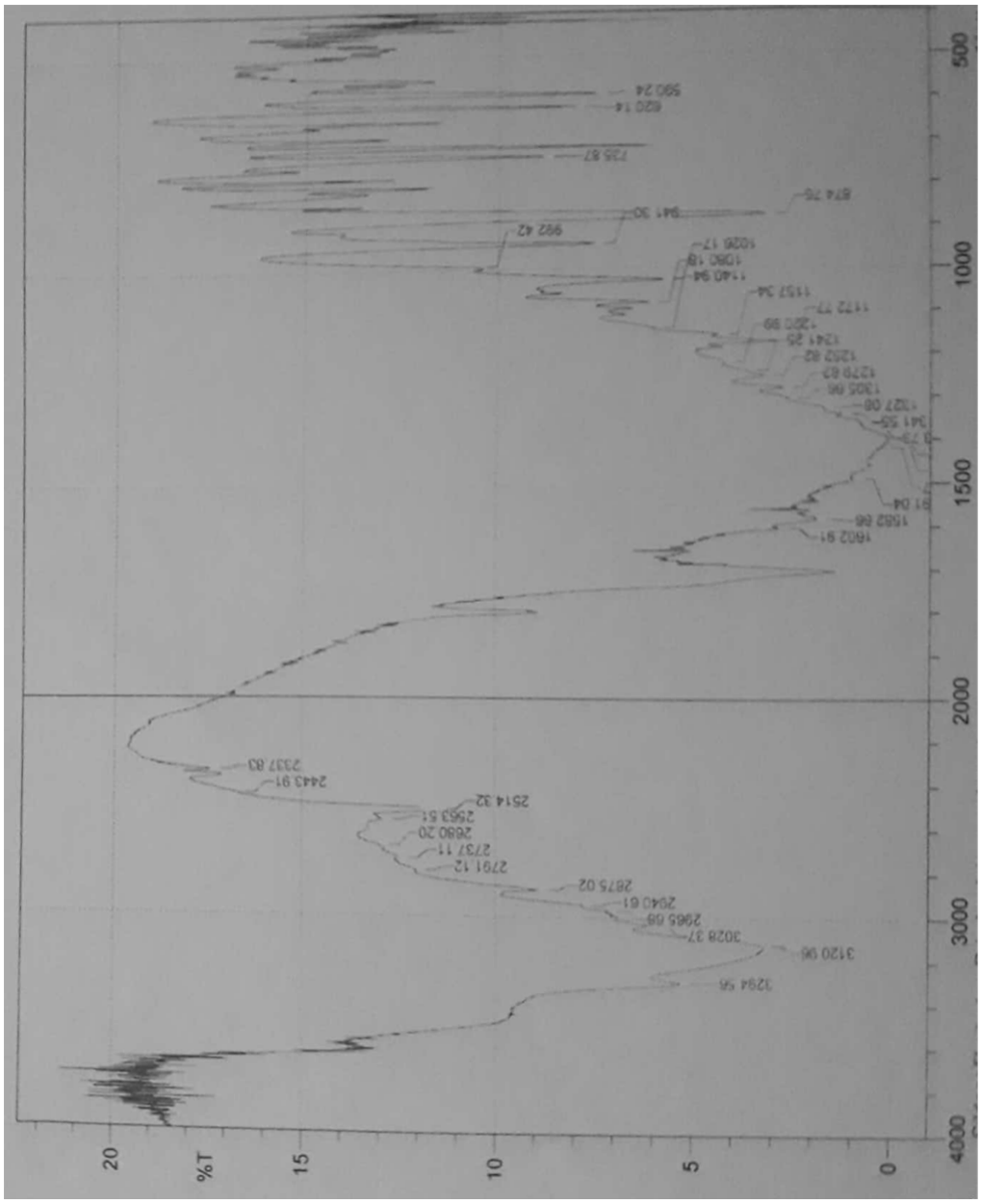


Figure no.6.5. I R spectra Sildenafil citrate+ pvp k 30

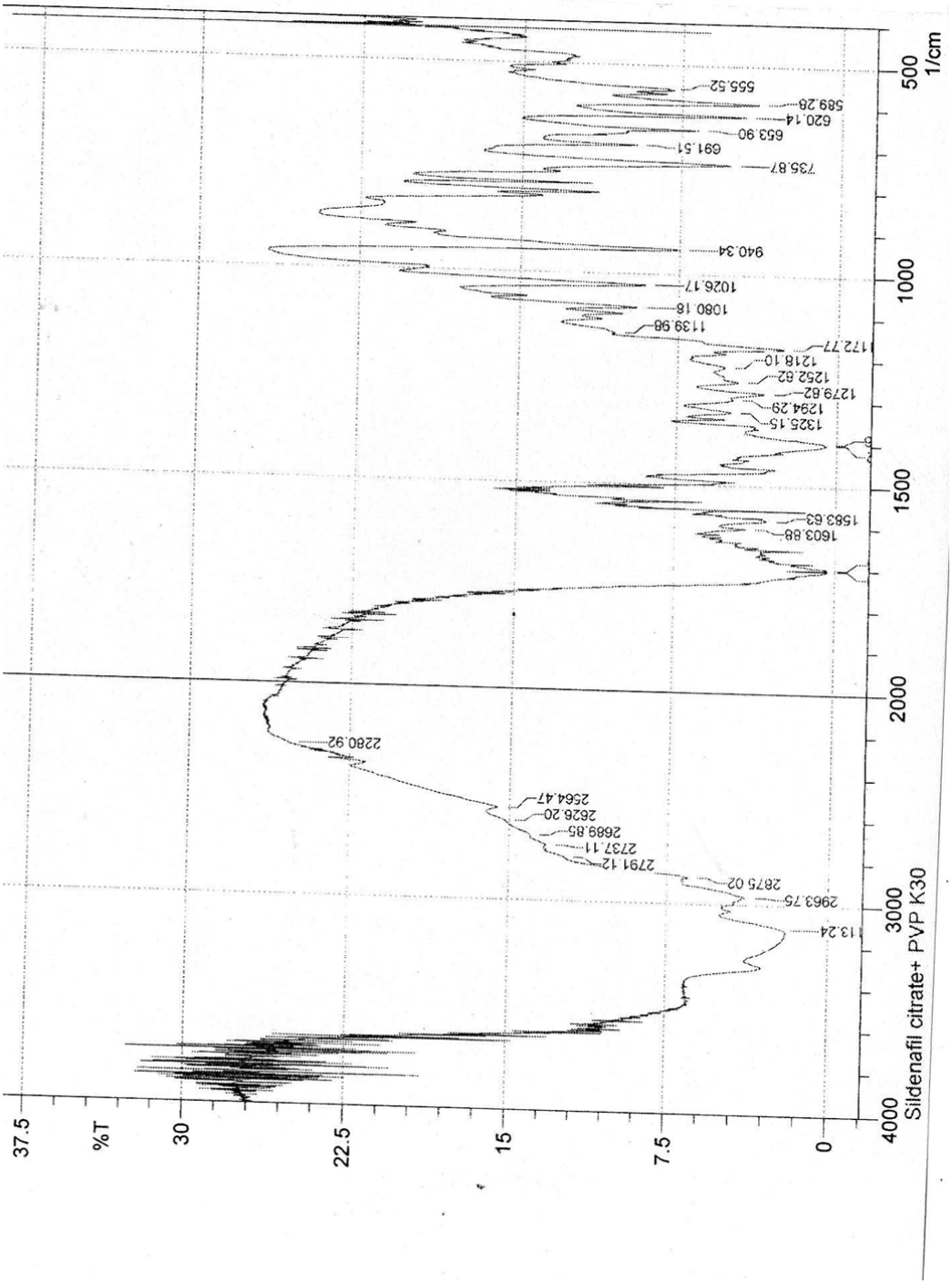


Figure no .6.6. I R Spectra of Sildenafil citrate+ crospovidone

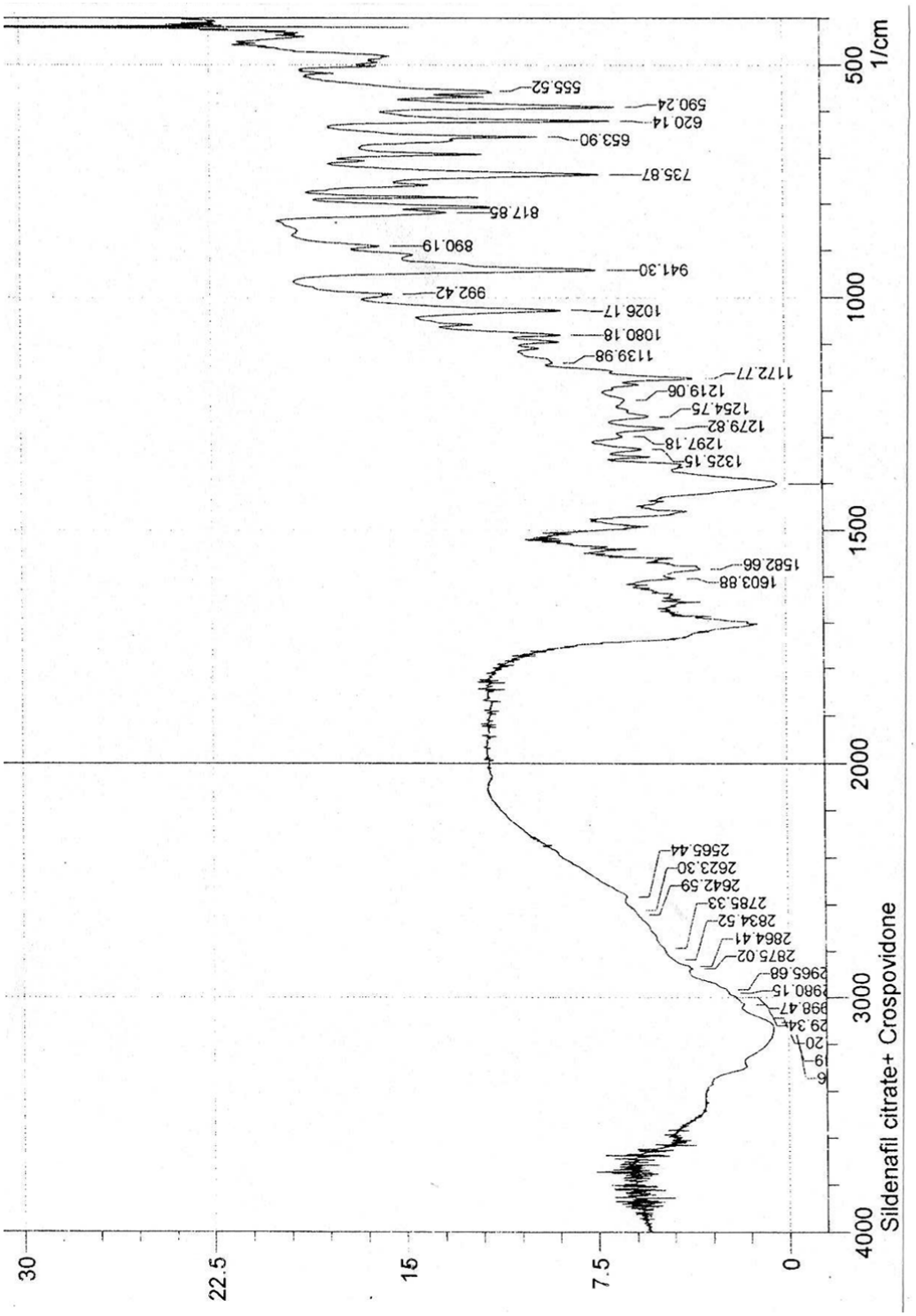


Figure no.6.7. I R Spectra of Sildenafil citrate+ croscarmellose sodium

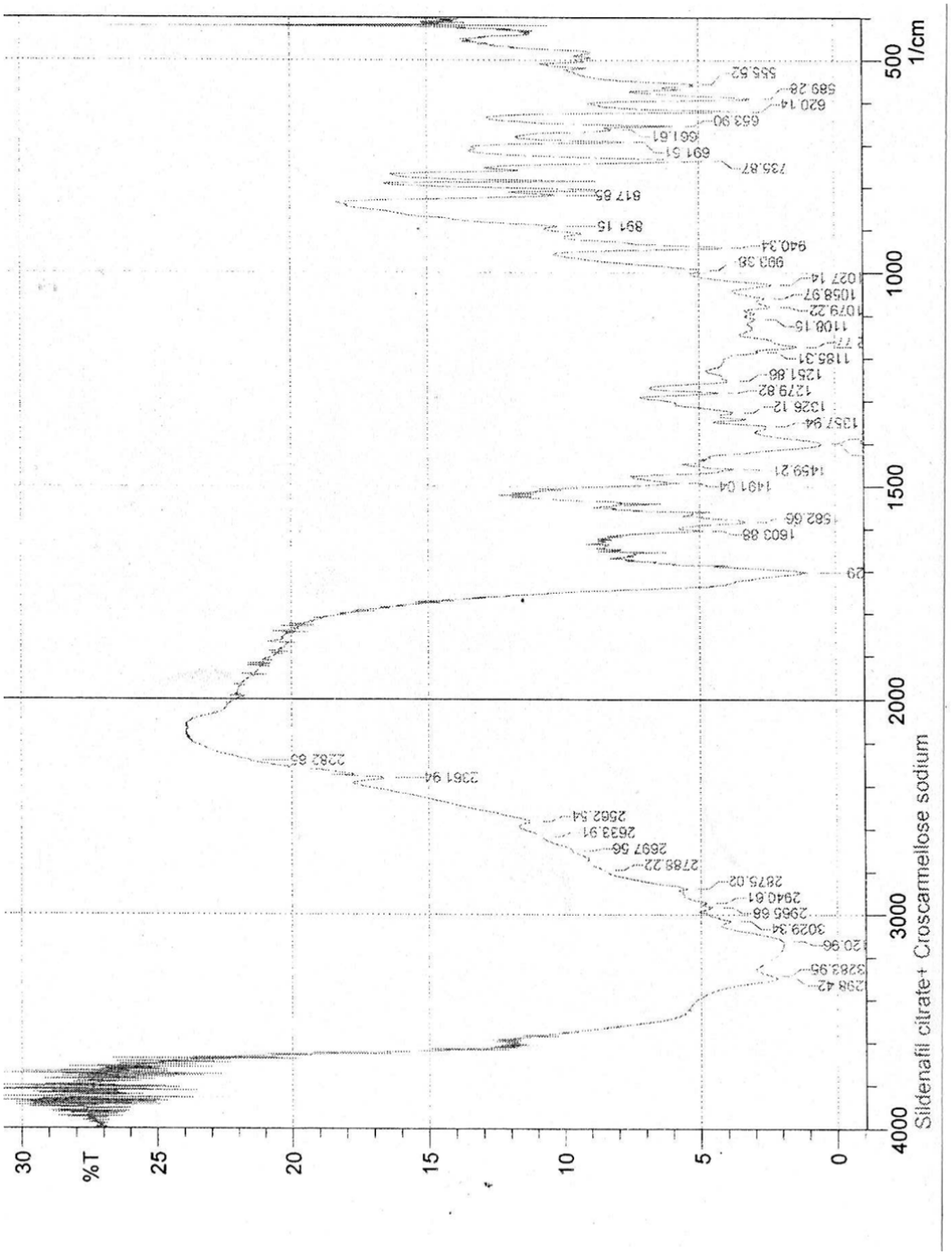


Figure no. 6.8. I R Spectra of Sildenafil citrate +aspartame

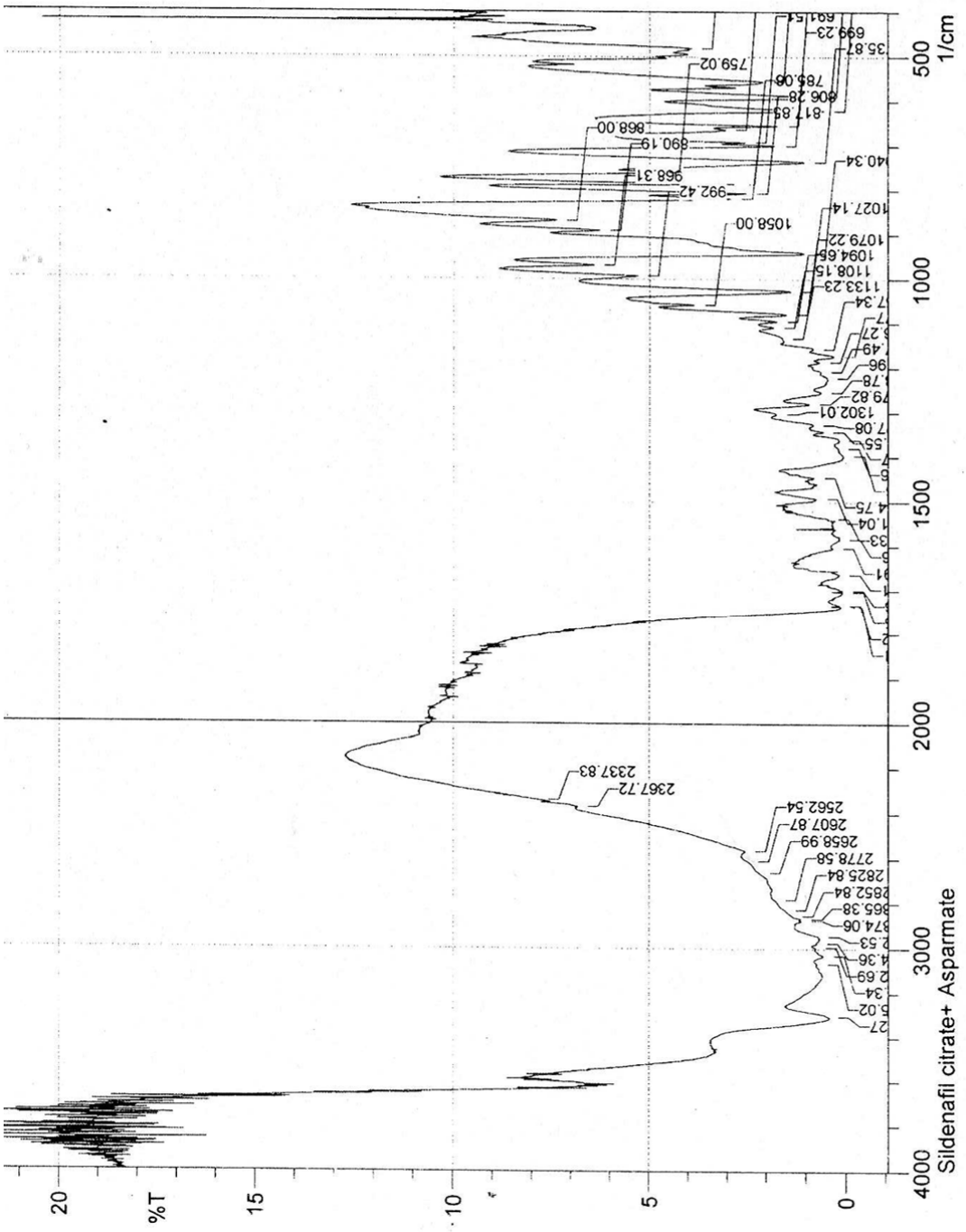


Figure no.6.9. I R Spectra of Sildenafil citrate + Aerosil

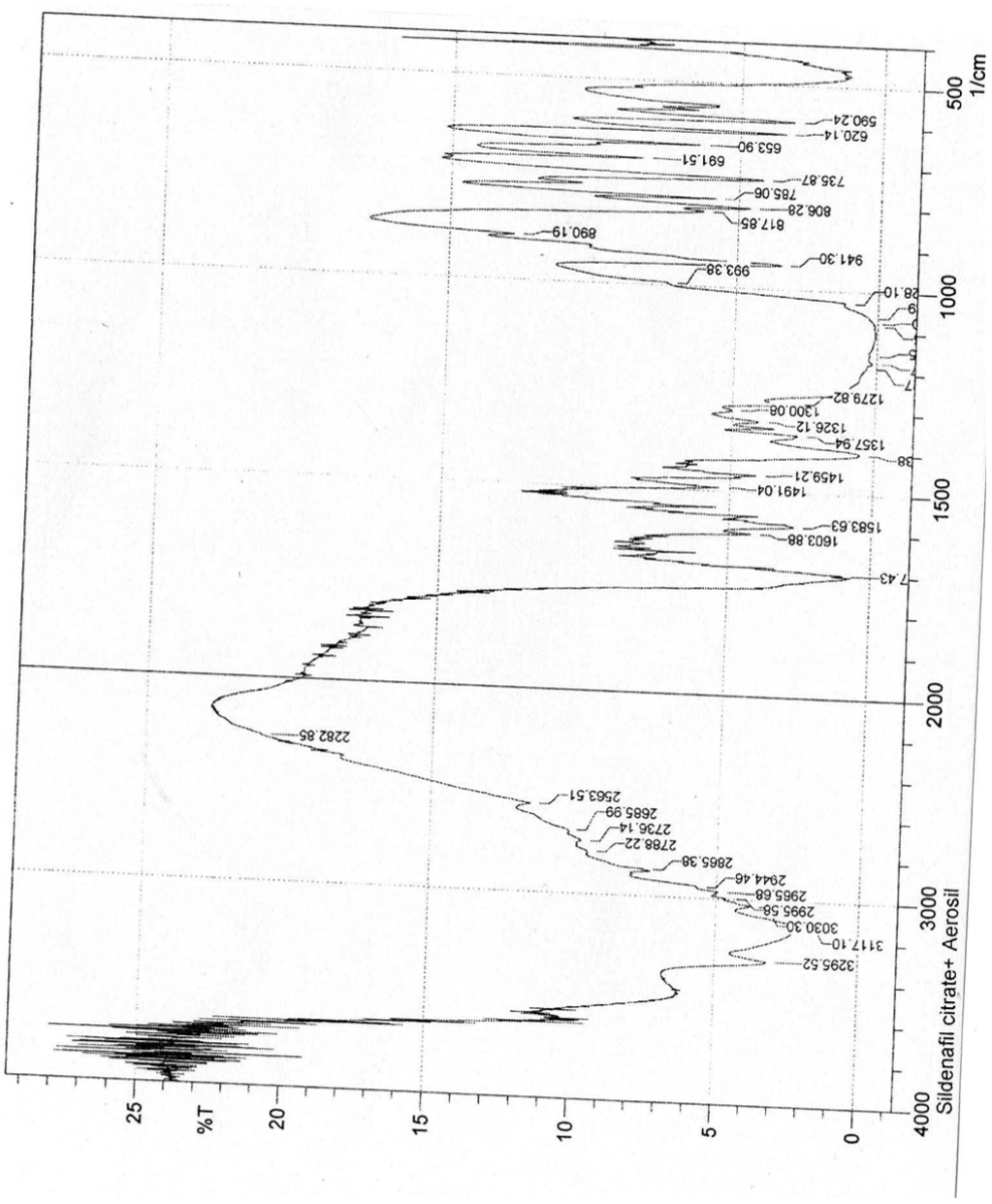


Figure no.6.10. Sildenafil citrate + blend

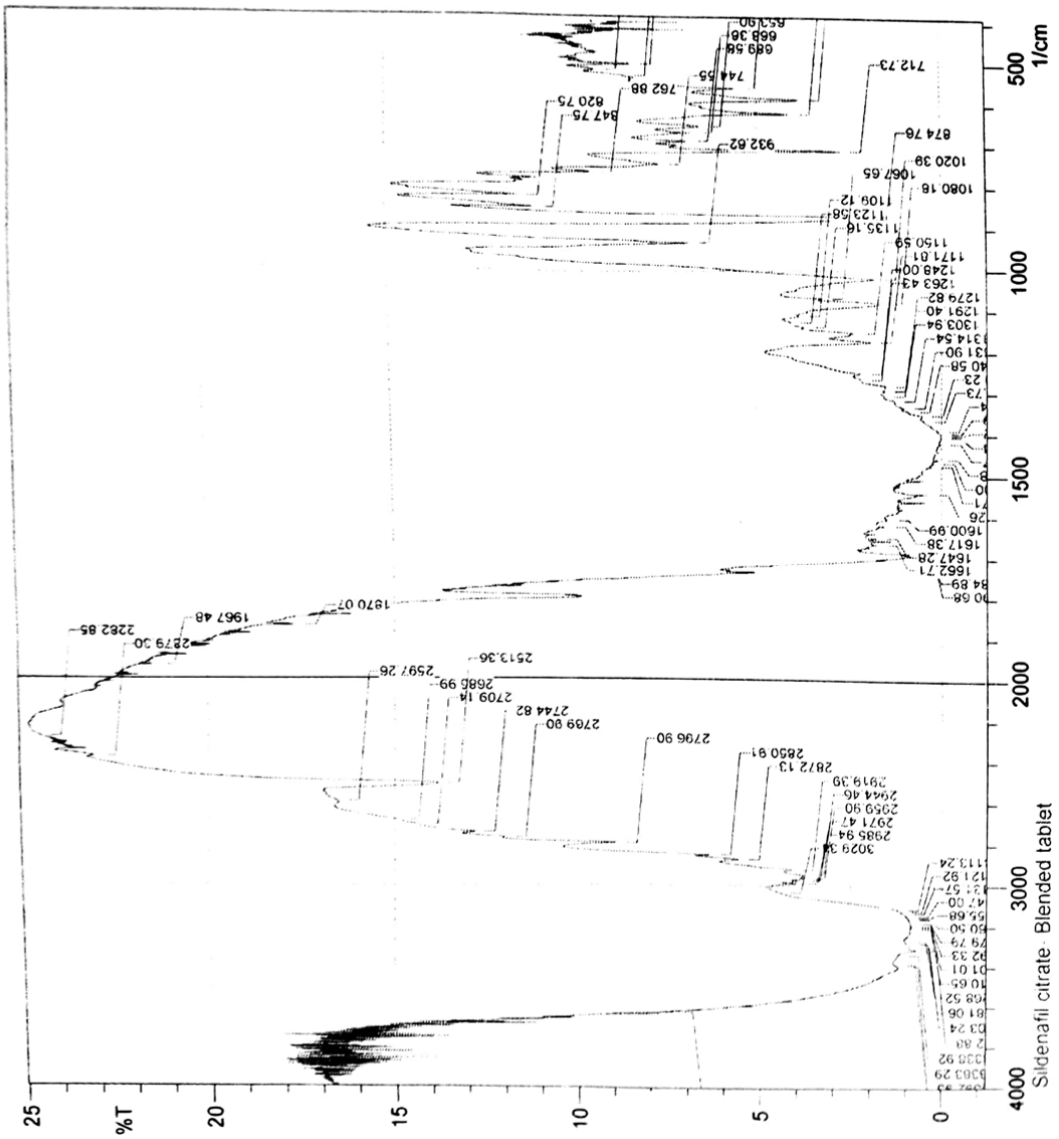


Table no.4.Sildenafil citrate pure drug peak

(wave number cm^{-1})	400-500	600-800	800-1000	1000-1200	1200-1400	1400-1600	1600-1800	2700-3000	3000-3700
Functional group	NH OH	$(CH_2)_4$ C=C C≡C AROMATIC	=CH C=C AROMATIC	AROMATIC PHENOL ALCOHOL AMINE	CH_3 AROMATIC PHENOL ALCOHOL AMINE NO_2	CH_3 AROMATIC PHENOL ALCOHOL AMINE NO_2	=CH C=C AROMATIC AMINE C=O	CH_3 CH_2 CH	=CH C=C ≡CH C≡C AROMATIC PHENOL ALCOHOL AMINE

Table no.5.Excipients peak

(wave number cm^{-1})	1700-2000	1700-2000	2000-2500	2500-3000	3000-3100
Functional group	=CH,C=C Aromatic Amine Ketone	=CH,C=C Aromatic Amine Ketone	ΞCH,CΞC CN	CH_3 CH_2 CH	=CH,C=C Aromatic Alcohol Phenols Amines

Table no.6.sildeanfil citrate + blend

(wave number cm^{-1})	400-500	600-800	800-1000	1000-1200	1200-1400	1400-1600	1600-1800	2700-33000	3000-3700	2000-2500	2500-3000	3000-3200
functional group	NH OH	$(CH_2)_4$ C=C C≡C AROMATIC	=CH C=C AROMATIC	AROMATIC PHENOL ALCOHOL AMINE	CH_3 AROMATIC PHENOL ALCOHOL AMINE NO_2	CH_3 AROMATIC PHENOL ALCOHOL AMINE NO_2	=CH C=C AROMATIC AMINE C=O	CH_3 CH_2 CH	=CH ,C=C Aromatic Amine ketone	ΞCH, CΞC CN	CH_3 CH_2 CH	=CH,C=C Aromatic Alcohol Phenols Amines

FT-IR on the selected formulation prepared with different excipients and polymer combination. The spectrum peak point of the formulation were similar with that of pure sildenafil citrate, it clear indicate that there are no excipients interaction.

Figure no.6.11 sildenafil citrate pure drug

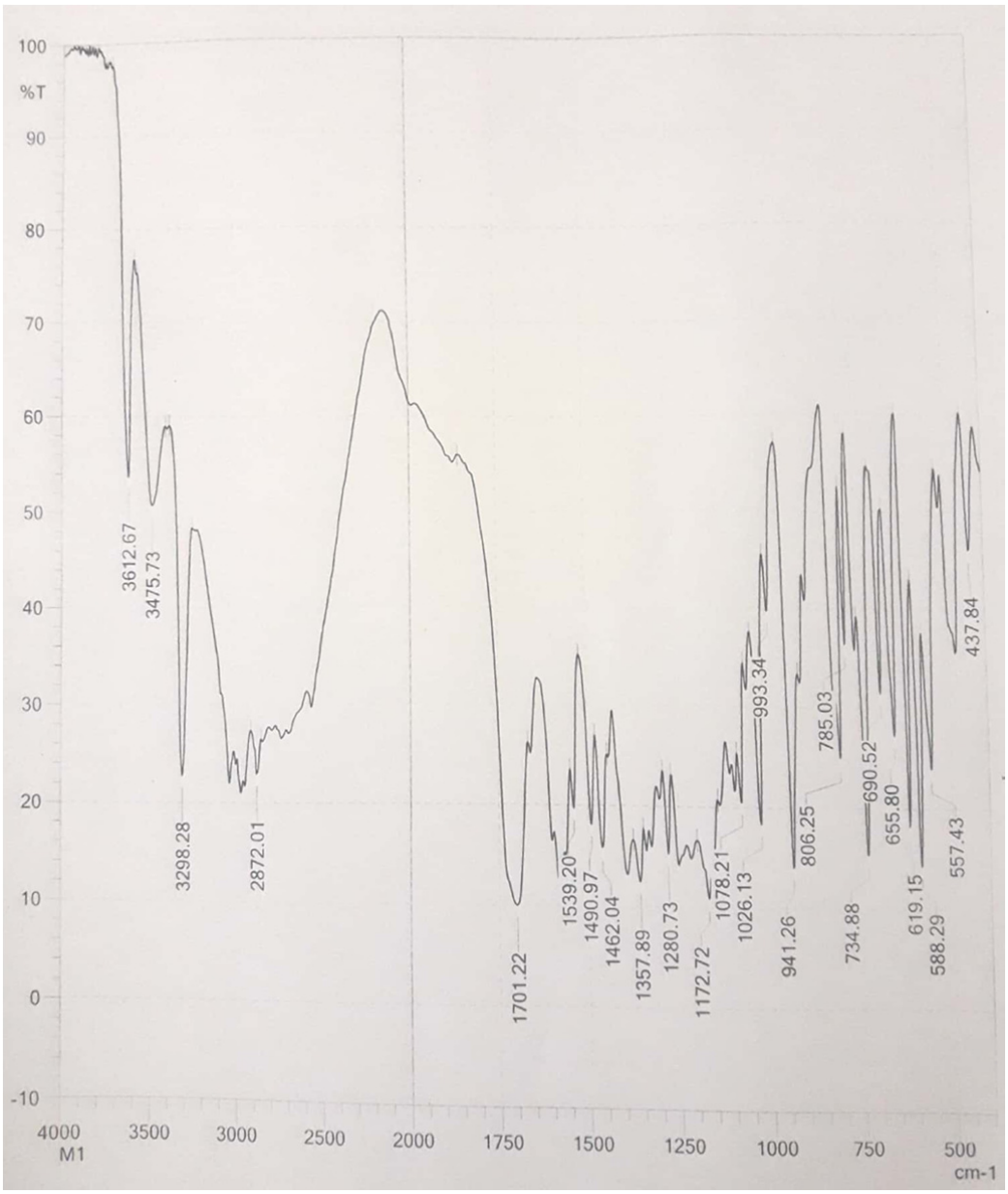


Figure no.6.12 Moringa gum

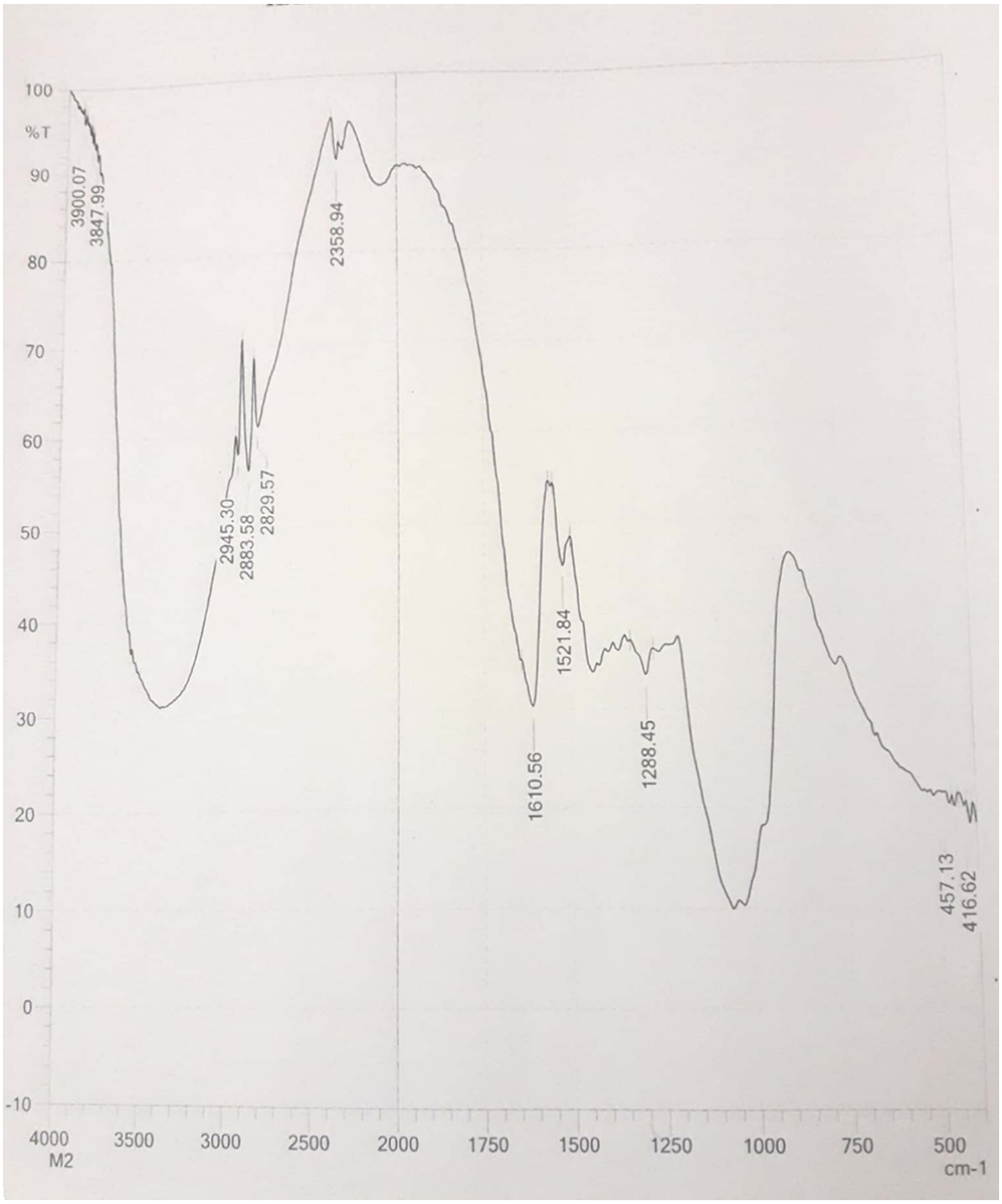


Figure no.6.13 sildenafil citrate +Moringa gum

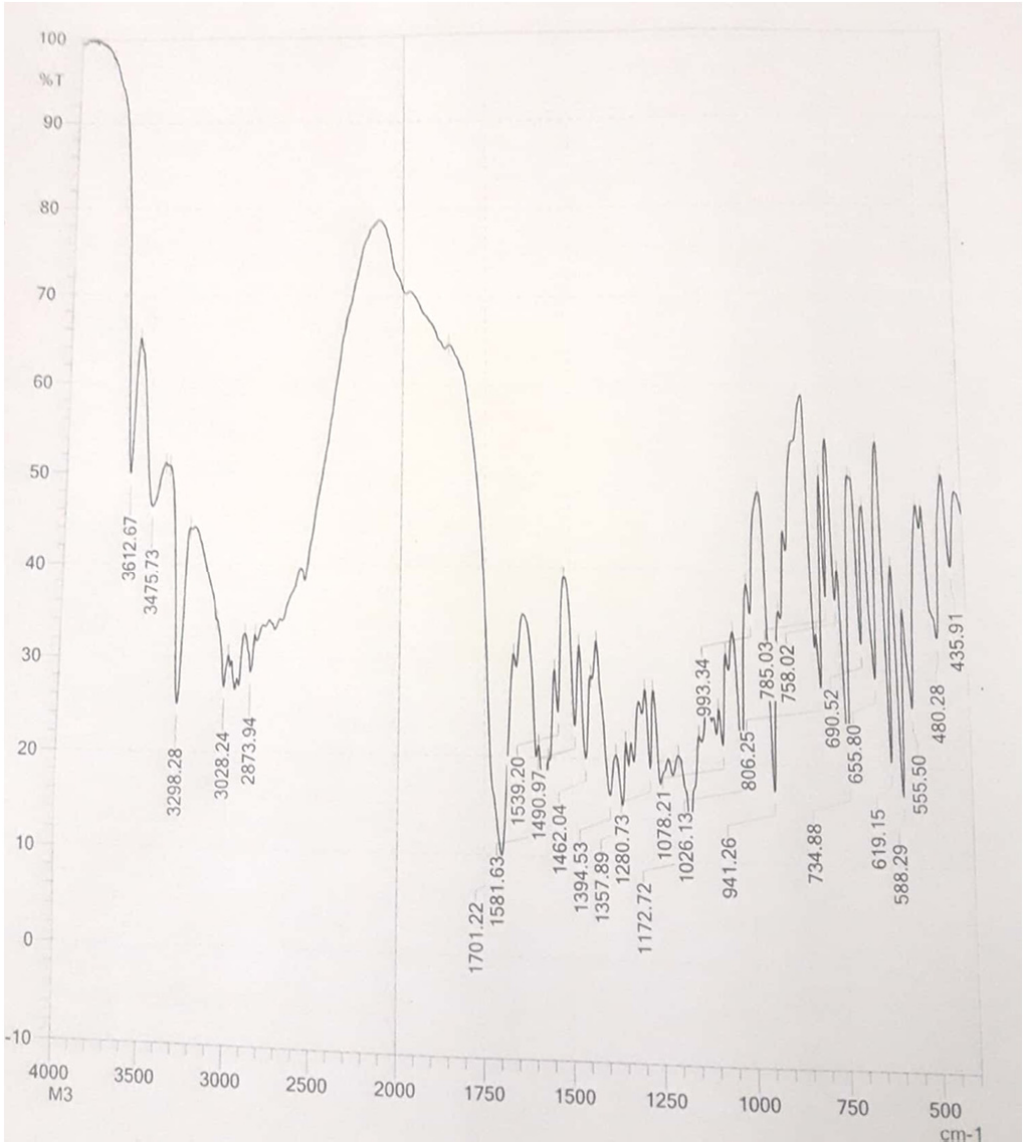


Figure no.6.14 sildenafil citrate + All excipients

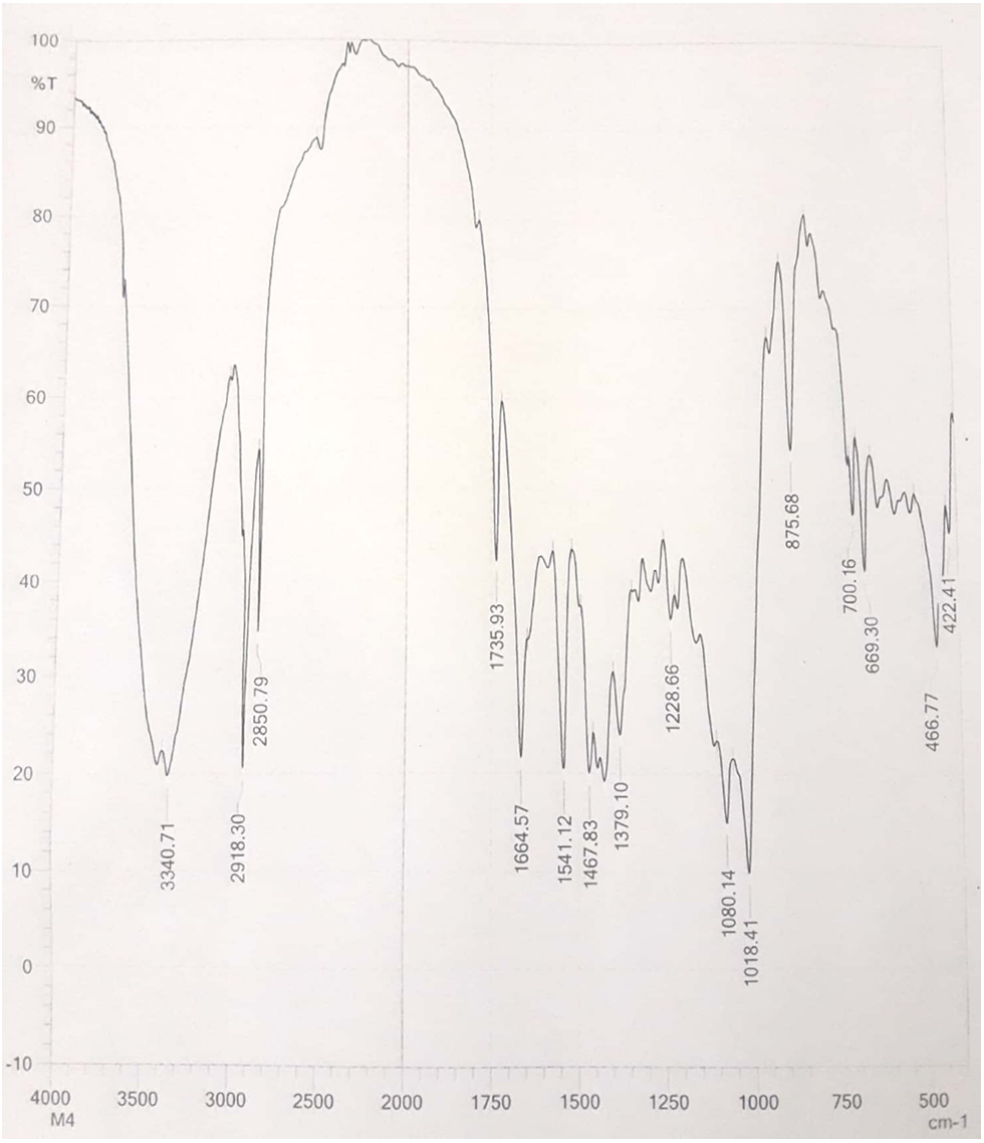


Table no.7.Sildenafil citrate pure drug

(wave number cm^{-1})	400-500	600-800	800-1000	1000-1200	1200-1400	1400-1600	1600-1800	2700-3000	3000-3700
Functional groups	NH OH	$(CH_2)_4$ C=C C≡C Aromatic	=CH C=C Aromatic	Aromatic Phenol Alcohol Amine	CH_3 Aromatic Phenol Alcohol Amine NO_2	CH_3 Aromatic Phenol Alcohol Amine NO_2	=CH C=C Aromatic Amine C=O	CH_3 CH_2 CH	=CH C=C ≡CH C≡C Aromatic Phenol Alcohol Amine

Table no.8.Moringa gum

(wave number cm^{-1})	400-500	1200-1600	2300-2400	2800-3000	3700-4000
Functional Groups	NH OH C=C	CH_3 CH_2 Aromatic Phenol Alcohol Amine NO_2	≡CH C≡C CN	CH_3 CH_2 CH	Phenol Alcohol

Table no.9.Sildenafil citrate with moringa gum

(wave number cm^{-1})	400-600	600-800	800-1000	1000-1200	1200-1400	1400-1800	2600-3000	3000-3400	3400-3800
Functional Group	NH OH C=C	$(CH_2)_4$ C=C C≡C Aromatic	=CH C=C Aromatic	Aromatic Phenol Alcohol Amine	CH_3 Aromatic Phenol Alcohol Amine NO_2	CH_3 Aromatic Phenol Alcohol Amine NO_2 =CH C=C Aromatic Amine C=O	CH_3 CH_2 CH	CH C=C Aromatic ≡C C≡C Phenol Amine	Phenol

Table no.10.Sidenafil Citrate with blend

(wave number cm^{-1})	400-600	600-800	800-1000	1000-1200	1200-1400	1400-1800	2700-3000	3000-3400
Functional Group	NH OH C=C	$(CH_2)_4$ C=C C≡C Aromatic	=CH C=C Aromatic	Aromatic Phenol Alcohol Amine	CH_3 Aromatic Phenol Alcohol Amine NO_2	CH_3 Aromatic Phenol Alcohol Amine NO_2 =CH C=C Aromatic Amine C=O	CH_3 CH_2 CH	CH C=C Aromatic ≡C C≡C Phenol Amine

FT-IR of the formulation and different excipients were prepared with KBr disc method. From the Figure 6.2 – 6.14 it was evident that the peak points of the formulation were similar with that of pure sildenafil citrate, it clearly indicate that there is no interaction of API with the excipients.

6.2. Evaluation of pre compression parameters for chewable tablet

Table no.11.pre-compression parameters for chewable tablet (direct compression)

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
F1	0.568	0.693	18.90	1.22	$25^{o}.12'$
F2	0.574	0.726	20.99	1.26	$27^{o}.31'$
F3	0.558	0.680	17.94	1.21	$29^{o}.46'$
F4	0.574	0.765	24.96	1.33	$25^{o}.71'$
F5	0.558	0.680	17.94	1.21	$23^{o}.86'$
F6	0.562	0.685	17.95	1.21	$24^{o}.71'$
F7	0.554	0.710	21.97	1.28	$25^{o}.10'$
F8	0.574	0.735	21.90	1.28	$28^{o}.14'$
F9	0.562	0.702	20.00	1.26	$28^{o}.14'$

6.2.1. Angle of repose.

All the formulation prepared by direct compression method showed the angle of repose between 25^{o} and 29^{o} excellent flow property it show in the above table.

6.2.2. Bulk density, tapped density, compressibility index and hausner's ratio.

The results of , Bulk density, tapped density, compressibility index and hausner's ratio are shown in the table no. 11.The bulk density and tapped bulk density for all formulation varied from 0.554 gm/cm^3 to 0.574 gm/cm^3 respectively. Tapped density for all formulation varied from 0.680 to 0.735 gm/cm^3. The result of Carr's consolidation index or (%) compressibility index for the entire formulation blend

ranged from 17 to 22 shows excellent compressibility index and hausner's ratio for all formulation varied from 1.21 to 1.33 which is an indicative of good flow property.

6.3. Post compression parameters

Table no.12.post compression evaluation parameters of chewable tablets

Formulation code	Average weight	Hardness (kg/cm^3)	Thickness (mm)	Friability	disintegration time (sec)	Wetting time (sec)	% Drug content
F1	701	5.68	5.18	0.134	90	60	99.2
F2	699	6.04	5.07	0.123	80	55	97.4
F3	700	5.54	5.22	0.093	65	50	99.6
F4	698	4.32	5.26	0.084	60	52	98.4
F5	700	4.10	5.17	0.124	40	45	99.3
F6	699	3.79	5.29	0.171	45	65	99.2
F7	698	3.05	5.20	0.138	70	59	100.1
F8	700	3.23	5.27	0.237	60	56	99.6
F9	698	3.38	5.31	0.264	78	50	99.6

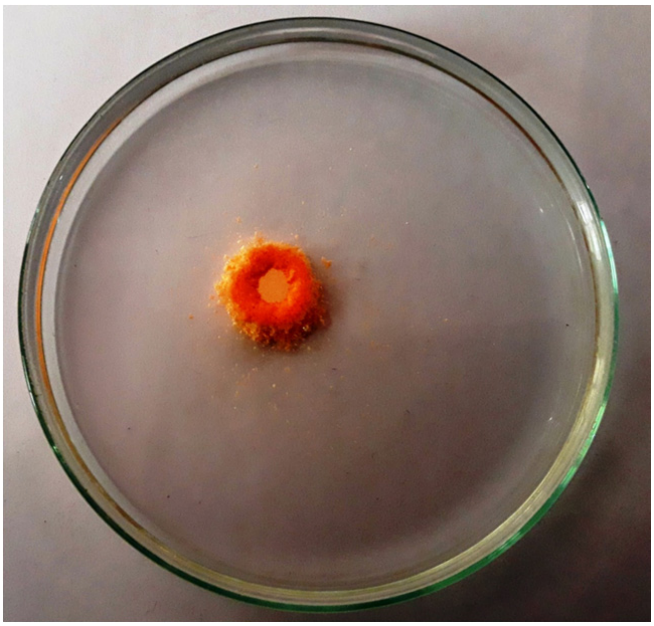
6.3.1. Post-compression evaluation of Sildenafil citrate

Average weight, Hardness test, Thickness test, Friability, Disintegration time, wetting time, Drug content.

The results of , Average weight,Hardness,Thickness,Friability,Disintegration time, wetting time ,Drug content are shown in the table no. 12.The bulk density and tapped density for all formulation varied from 698mg to 701 mg . All the formulations passed the weight variation test as results were found to be IP limits of ±5% weight. The maximum thickness of the formulation was found to be 5.29 ± 0.005 mm in batch F6 and minimum thickness of the was found to be 5.07 ± 0.001 mm in batch F2. The hardness of all the formulation tablets were determined by Pfizer

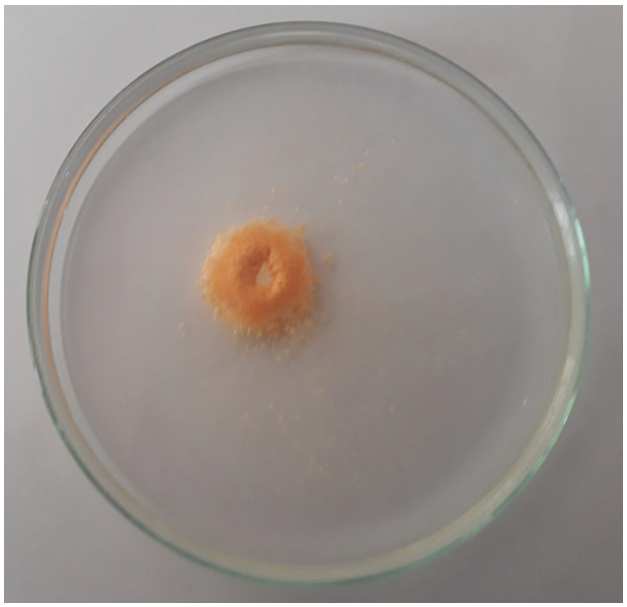
hardness tester and it was found to be in the range of 3.05 ± 0.01 to 6.04 kg/cm^3. Friability of the various batches was found to be in between 0.264 ± 0.14% to 0.084 %. Wetting time for all formulated tablet were found to be in the range of 40.01 ± 0.056 to 90.0 ± 0.56 seconds. The wetting time for tablets closely relate to the pore size of the internal structure, which affects the penetration of water into the tablets. The maximum percentage of the drug content of the formulation was found to be 100.1 ± 0.33 and maximum percentage of the drug content from all formulation was found 98.4 ± 0.46, ensuring the uniformity of the drug content in the all formulations.

Figure no 6.15 wetting time for sildenafil citrate F5



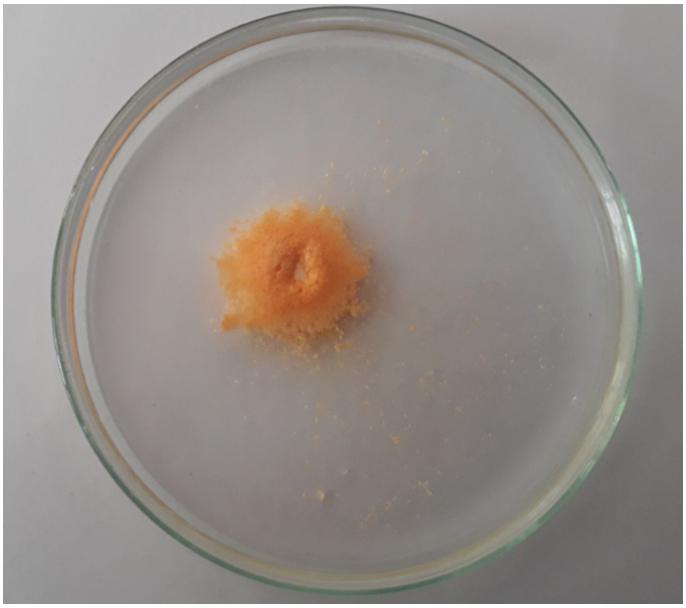
Sildenafil citrate tablets after 5 seconds

Figure no 6.16 wetting time for Sildenafil citrate F5



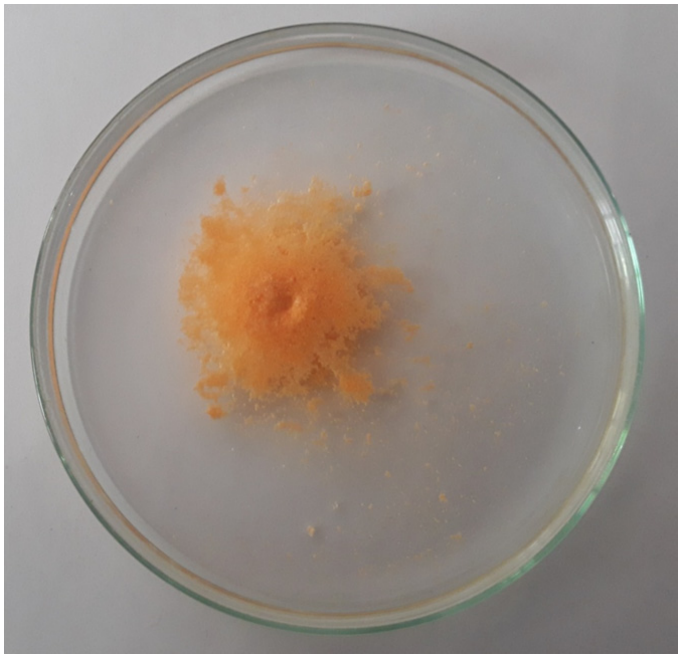
Sildenafil citrate tablets after 15 seconds

Figure 6.17 wetting time for sildenafil citrate F5



Sildenafil citrate tablets after 25 seconds

Figure no 6.18 wetting time for sildenafil citrate F5



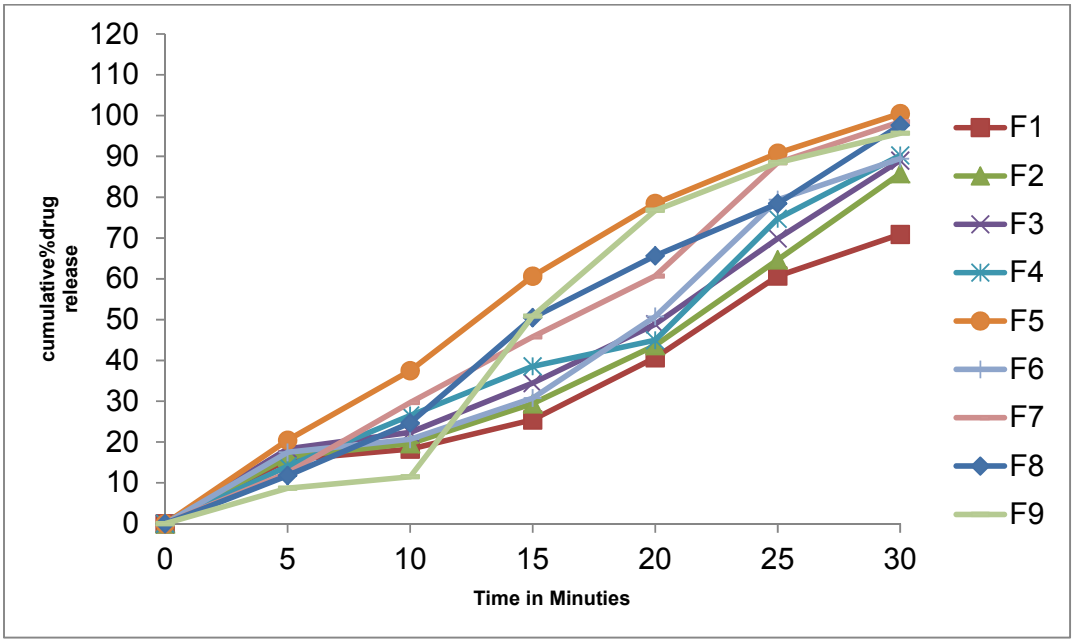
Sildenafil citrate tablets after 40 seconds

6.4. Dissolution data for chewable tablet

Table no.13. Dissolution data of chewable tablets

Time in min	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	15.65	16.32	18.35	14.06	20.48	17.48	12.48	11.79	8.69
10	18.28	19.62	22.35	26.50	37.49	20.68	29.68	24.69	11.49
15	25.45	29.40	34.45	38.56	60.67	30.78	45.78	50.48	50.87
20	40.67	43.67	48.87	44.96	78.48	50.78	60.68	65.67	76.79
25	60.70	64.68	69.89	74.74	90.79	79.40	88.48	78.45	88.48
30	70.89	85.78	88.98	90.25	100.5	89.45	98.48	97.65	95.67

Figure no 6.19 Dissolution Profile



6.5. Dissolution graph for chewable tablet

All the formulations except batch F5 were not able to release 100 % of drug within 30 minutes. F5 formulation released the total drug within 30 minutes which will aid in the fast onset of action. This may be attributed to the presence of super disintegrants croscarmellose sodium and crospovidone in batch F5. This also might have increased by the increased wetting of the tablet resulting in fast dissolution.

6.5.1 Comparison of optimized formulation (f5) with innovator product (Viagra 100mg by marketed tablet)

The optimized formulation (F5) was compared with innovator product, Viagra 100mg for in-vitro disintegration and dissolution studies. The in-vitro disintegration time of F5 formulation was found to be 40 seconds and that of Viagra was found to be 80 seconds. The in-vitro disintegration time of optimized formulation was found 6 times lesser than the innovator product. The dissolution time of F5 was found to be 100.5% in 30 minutes, where as the marketed product showed 98.08 % of drug release in 30 minutes. This indicates formulation F5 showed rapid release of the drug than the innovator product.

Table no.14. Comparison of formulation tablet vs marketed tablet

FORMULATION	CUMULATIVE % DRUG RELEASE						
	0min	5min	10min	15min	20min	25min	30min
F5	0	20.48	37.49	60.67	78.48	90.79	100.5
Viagra	0	16.67	30.76	58.78	70.54	86.78	98.08

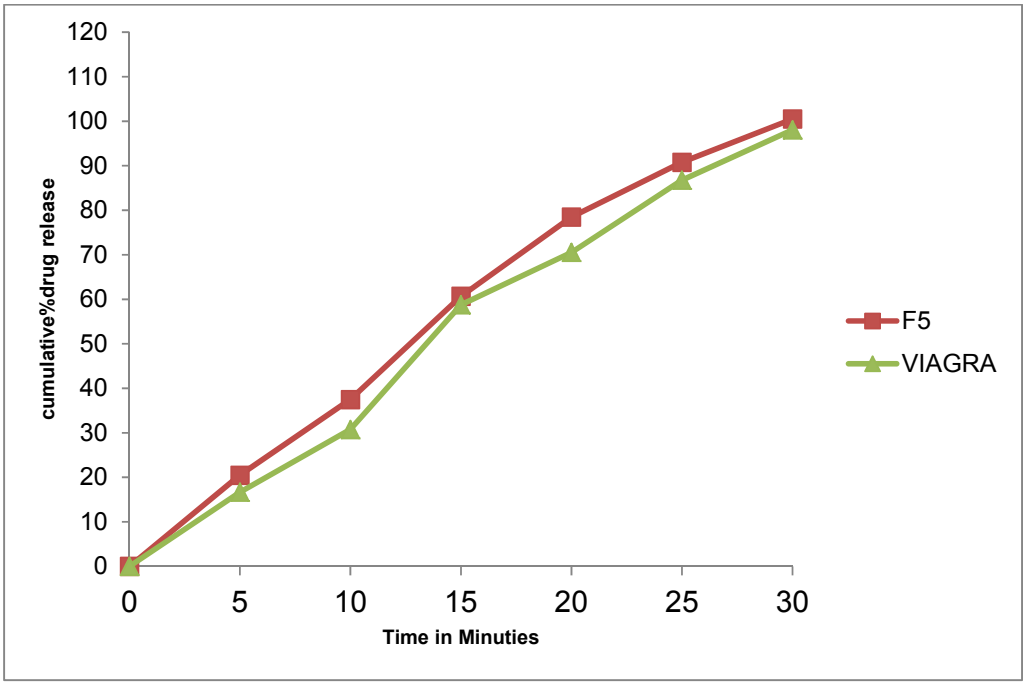


Figure no 6.20. Comparison of marketed tablet vs. sildenafil citrate F5 batch

6.5.2. Stability studies

Evaluation of tablet parameters after stability studies at storage condition- 40^0C/75%RH Period-3Month

Table no.15. Stability studies

S.no.	Parameter	Time duration			
		0Month	1Month	2Month	3Month
1	Physical character	--	--	--	--
2	Friability%	0.42	0.45	0.45	0.42
3	Hardness[kg/^{cm3}]	6.85	6.81	6.82	6.84
4	% drug release of at 30min	100.5	100.25	99.04	98.12

6.5.3. Evaluation of pre compression parameters for batches with moringa gum by wet granulation method.

Table no.16.pre-compression parameters for chewable tablet (wet granulation method)

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose
F10	0.558	0.685	17.94	1.21	$26^{o}.12'$
F11	0.554	0.680	18.90	1.33	$27^{o}.71'$
F12	0.560	0.726	21.90	1.28	$29^{o}.46'$

6.5.4. Angle of repose.

All the formulation prepared by wet granulation method showed the angle of repose between 26^{o} and 29^{o} revealing excellent flow property as shown in the table no 16.

6.5.5. Bulk density, tapped density, compressibility index and hausner's ratio.

The results of, Bulk density, tapped density, compressibility index and hausner's ratio of batches prepared by wet granulation method are shown in the table no. 16. The bulk density and tapped bulk density of the formulation varied from 0.554 gm/cm^3 to 0.560 gm/cm^3 respectively. Tapped density for all formulation varied from 0.680 gm/cm^3 to 0.726 gm/cm^3. The result of Carr's consolidation index or (%) compressibility index for the entire formulation blend ranged from 17 to 21 shows excellent compressibility index and hausner's ratio for all formulation varied from 1.21 to 1.33 result in good flow properties.

6.5.6. Post compression parameters

Table no.17. Post compression evaluation parameters

Formulation Code	Avg. Weight	Hardness (kg/cm^2)	Thickness (mm)	Friability	Disintegration time (sec)	Wetting time (sec)	%Drug content
F10	701	4.85	4.28	0.026	35	55	99.48
F11	699	4.81	4.41	0.021	25	58	97.56
F12	700	6.80	4.32	0.022	20	45	95.46

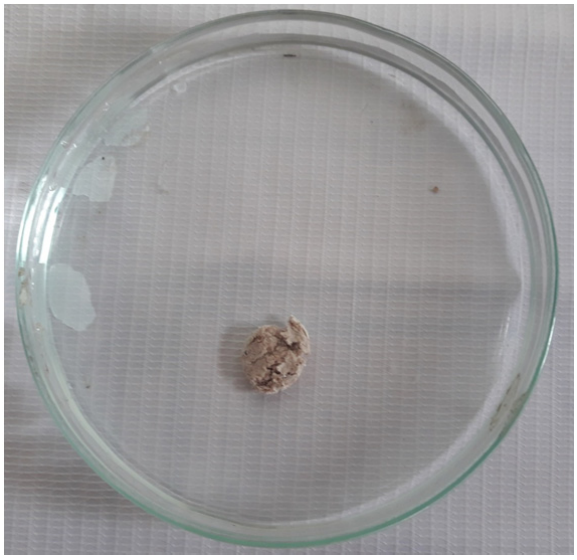
6.5.7. Post-compression evaluation of Sildenafil citrate

Average weight, Hardness test, Thickness test, Friability, Disintegration time, Wetting time, Drug content.

The results of, Average weight, Hardness, Thickness, Friability, Disintegration time, wetting time ,Drug content are shown in the table no.17. The average weight of the tablet varies from 699 mg to 701mg. All the formulation passed the weight variation test as results were found to be IP limits of ±5% weight. The maximum thickness of the formulation was found to F10 batch 4.28 ± 0.005 mm minimum thickness of the batch F11 was found to be 4.41±0.001mm F11.The hardness of all the formulation tablets were determined by Pfizer hardness tester and it was found to be in the range to be in the range of 4.80 ± 0.01 to 6.04kg/cm^3.The Friability of the all formulation tablet were determined by Roche friabiliators found to be in between 0.021±0.14% to 0.026%. Wetting time for all formulated tablet were found to be in the range of 0.50±0.056 to 0.38±0.56 minuties. The wetting time for tablets closely releated to the pore size of the internal structure .which is affected the penetration of water into the tablets. The maximum percentage of the drug content of the formulation was found to be 99.48±0.33 and maximum percentage of the drug content

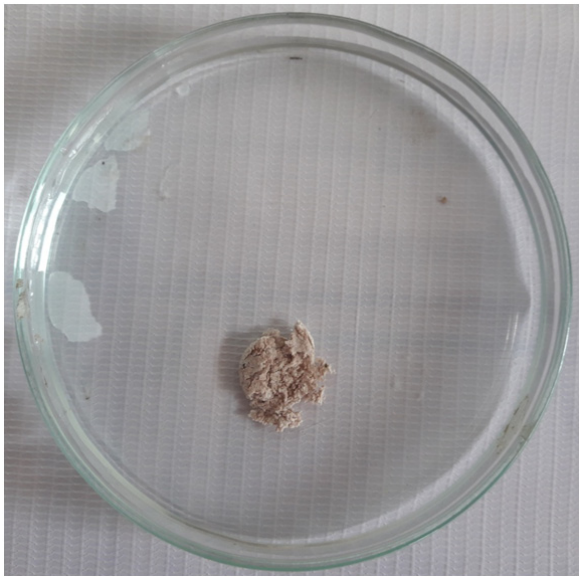
from all formulation was found 95.46±0.46, ensuring the uniformity of the drug content in the all formulations.

Figure no.6.21.Wetting time for sildenafil citrate F12



Wetting time for Sildenafil citrate 20seconds

Figure no.6.22.Wetting time for sildenafil citrate F12



Wetting time for sildenafil citrate 30 seconds

Figure no.6.23.Wetting time for sildenafil citrate F12

Wetting time for sildenafil citrate 45 seconds

6.6. Dissolution data for sildenafil citrate

Table no.18. Dissolution data of sildenafil citrate

TIME IN MIN	F10	F11	F12
5	10.54	15.45	20.65
10	25.54	30.65	38.46
15	45.01	50.84	69.01
20	75.65	78.45	82.98
25	85.78	90.05	95.78
30	95.09	98.05	100.98

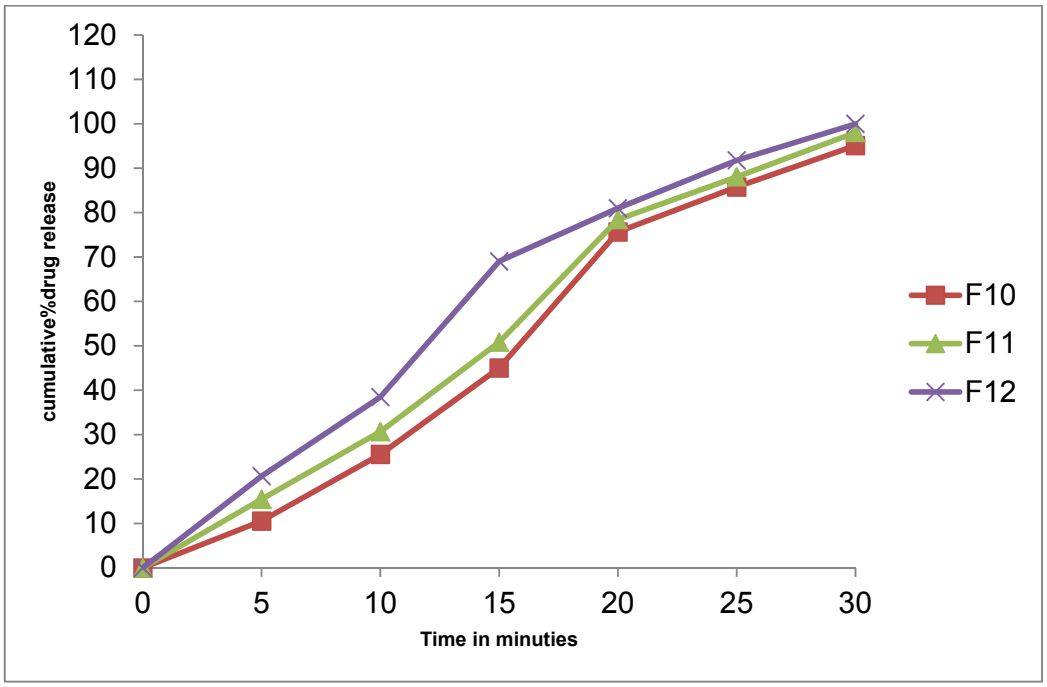


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Figure no .6.24 Dissolution profile

6.7. Dissolution graph for Wet granulation method for sildenafil citrate

The batch F12 released 100 % of the drug within 30 minutes. Hence increasing the concentration of moringa gum resulted in the reduction of disintegration time and increase of dissolution and wetting time. Hence moringa gum can be suitably used with sildenafil citrate as a disintegrating agent for increasing the onset of action.

Table no.19. Comparison of formulation tablet vs marketed tablet

FORMULATION	CUMULATIVE % DRUG RELEASE						
	0min	**5min**	**10min**	**15min**	**20min**	**25min**	**30min**
F12	0	20.65	38.46	69.01	80.98	91.78	100.98
Sildenafil citrate	0	18.02	35.67	62.03	77.04	80.43	95.08

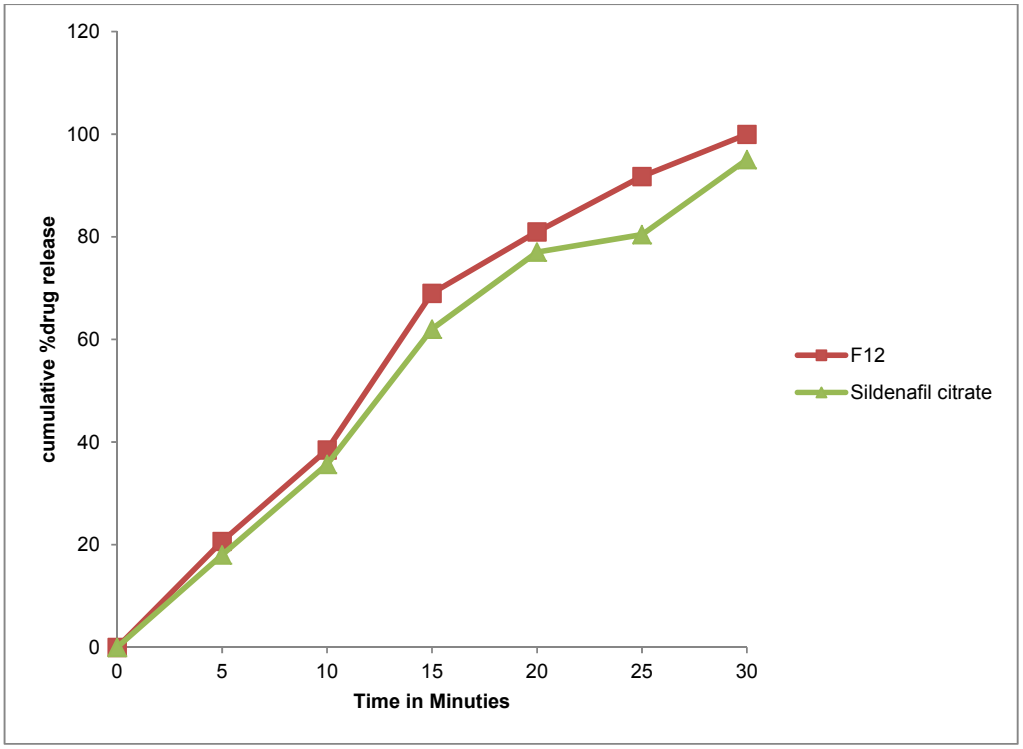

Figure no.6.25. Comparison of marketed tablet vs Sildenafil citrate

6.8. Comparison of Optimized formulation (F12) with Innovator Product (Sildenafil citrate 100mg by marketed tablet)

The optimized formulation (F12) was compared with innovator product, Viagra 100mg for in-vitro disintegration and dissolution studies. The in-vitro disintegration time of F12 formulation was found to be 20 seconds and that of Viagra was found to be 80 seconds. The in-vitro disintegration time of optimized formulation was found 6 times lesser than the innovator product. The dissolution time of F12 was found to be 100.98 in 30 minutes, where as the marketed product showed 95.08 % of drug release in 30 minutes. This indicates formulation F12 showed rapid release of the drug than the innovator product.

CHAPTER 7
SUMMARY AND CONCLUSION

7.1. SUMMARY AND CONCLUSION

- The chewable tablets of taste masked sildenafil citrate were successfully prepared by direct compression method and wet granulation method.
- 12 batches using various additives were prepared and evaluated with an aim of presenting sildenafil citrate taste masked by the chewable tablet.
- Drug excipient compatibility study was performed by FTIR.
- The unpleasant taste of the sildenafil citrate was masked by intra-granular addition of dried calcium carbonate, calcium carbonate from oyster shell and the extra-granular addition of sweeteners and flavoring agents. Taste masking study was done by using alkalizing agent in different ratio. Sildenafil citrate taste masking was increased when dried calcium carbonate quantity was increased because of reduction of the solubility of sildenafil citrate. Oyster shell calcium carbonate when added to the drug did not masked the taste due to the gritty nature of it.
- F5 batch showed less bitterness, low disintegration time and fast dissolution time and hence was taken further comparing with the innovator drug.
- In the present study disintegrating properties of Moringa Oleifera gum powder had been studied in comparison with other commercially available super disintegrants. The isolated natural disintegrant exhibits faster drug dissolution and disintegration. The isolated gum powder can be effectively used as disintegrant for sildenafil citrate with the added advantage of the folkloric aphrodisiac activity of it.
- The physicochemical evaluation results for the powdered blend of all trials pass the official limits in the angle of repose, compressibility index, Bulk density, Tapped density, Hausner's ratio.

- Hence it may be summarized that the tablets prepared by direct compression method might be a perfect and effective formulation to prevent the side effects in treating erectile dysfunction".

CHAPTER 8
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