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FORMULATION DEVELOPMENT AND EVALUTION OF MEDICATED CHEWING GUM OF AVANAFIL

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ABSTRACT

Medicated chewing gum- A growing trend in pharmaceutical world.

Introduction: Medicated chewing gum is defined as a single solid dosage form containing active ingredient along with the excipients which is intended to be chewed for the release of the active ingredient and rest mass to be discarded out. Medicated chewing gums are usually used to treat diseases related to mouth, throat or for Erectile dysfunction. Avanafil being a Phosphodiesterase-5 (PDE-5) Inhibitor drug which is used for erectile dysfunction. Avanafil have faster onset of action as well as higher specificity for phosphodiesterase type 5 inhibitors with fewer side effects in comparision of other oral phosphodiesterase type 5 inhibitors drugs.

Objectives: Avanafil being a BCS class II drug shows less of absorption and bioavailability. Medicatedchewing gum overcomes such problems and which also increases the patient compliance.

Materials and Methods, Evaluation and Conclusion: Avanafil along with Polyvinylacetate, Sucrose, Peppermint flavour, Glycerine, Calcium Carbonate, Aspartame, Mannitol, ß-cyclodextrin (ß-CD) was used to formulate the medicatedchewing gum. Preliminary batches were prepared with a deep literature survey and best batch from it was selected for optimization of further batches. Evaluation was carried out of the formulated batches along with the stability studies and buccal permeation showing satisfactory results. Thus formulation of Avanafil into medicated chewing gum was done successfully.

KEYWORDS: Medicated chewing gum, Avanafil, Erectile dysfunction, fast onset of action, increase in bioavailability, % drug content, % drug release.

1. INTRODUCTION

1.1 Erectile Dysfunction (Ed)[1]

- Erectile dysfunction (ED), one of the most common sexual disturbances in the adultmale.
- It is defined as a man's consistent or recurrent inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance.
- Erectile dysfunction increases by their growing ages.

1.1.1 Epidemiology

- The definition for erectile Dysfunction portrays the commonness of sexual brokenness which was 1-10 percent in men amid his young age at 40 years.
- Incidence of sexual dysfunction which sort from 2-19 percent in men during his ages at40 to 49 years.
- Then it is upsurges from 20-40 percent in men aged at 60-69 years.
- If the men consist of more than 70 years, the prevalence of sexual dysfunction contain 50 to 100 percent.

1.1.2 Causes of Erectile dysfunction[2]

- The penis does not accept sufficient blood to obtain an erection.
- The sexual dysfunction occurs repeatedly and affects man's ability to sustain an activesex life.
- It can causes both frustrating and embarrassing for man to have sexual dysfunction.

1.1.3 Oral Drug Delivery System[3]

Among the various routes, Oral route is most preferred for drug administration. Most of the drugs are being taken in the form of tablets and capsules by all patients, including adult, pediatric and geriatric patients. It is estimated that many patients find it difficult to swallow tablets and capsules. Many pharmaceutical companies have directed their research activity in reformulating existing drugs into new dosage forms. One such dosage form is MEDICATED CHEWING GUM (MCG).

Fig 1.1: Different pharmaceutical dosage forms.

Pharmacological active agents or drugs are formulated into variety of dosage forms like tablets, capsules, injectables, inhalers, ointments etc., by considering physicochemical properties, pharmacokinetic and pharmacodynamic parameters and biopharmaceutical aspects of drugs. Chewing gums are interesting as an alternative drug delivery system when considering oral or per oral administration of drug substances since they may offer a number of advantages over conventional dosage forms. They are considered as mobile drug delivery systems having convenient and individually controlled release of the active substance, effective buccal drug administration for treatment of local oral or throat diseases.

Fig 1.2: Oral route of administration.

The European Pharmacopeia characterizes cured biting gums as „„solid, single-portion arrangements with a base comprising essentially of gum that are proposed to be bitten yet not gulped. Sedated Chewing Gum is a novel medication conveyance framework containing masticatory gum base with pharmacologically dynamic fixing and planned to use for nearby treatment of mouth sicknesses, throat maladies or fundamental assimilation through oral or throat mucosa. MCG is considered as vehicle or a medication conveyance framework to manage dynamic rules that can enhance wellbeing and nourishment.

1.1.4 Advantages

- Easy for administration.
- Higher patient compliance.
- Fast onset of action.
- Less side effect.
- Dose not requires water to swallow.
- Beneficial for patients having trouble in swallowing.
- Retain a good stability.
- Counters thirsty mouth, averts candidiasis and caries.
- Extremely satisfactory by children.
- Escapes First Pass Metabolism and thus upsurges the bioavailability of drugs.

1.1.5 Other Advantages

- Relaxes and eases tension.
- Freshens the breath.
- Decreases ear discomfort when flying.
- Satisfies snack craving.
- Cleans teeth after meals.

1.1.6 Limitations

- Cause flatulence and diarrhoea because of sorbitol.
- Causes ulcers in oral cavity because of flavouring agent presents like cinnamon.
- Produces staining on teeth and tongue.
- Causes hypertension because of liquorice.

1.1.7 Method of Preparation of Medicated Chewing Gum[3,4]

Fig 1.3: Different types of medicated chewing gums.

1. Conventional/Traditional method (Fusion)

Components like sweeteners, syrups, active ingredients and other excipients are added at a definite time by the. gum base are softened or melted and placed in a kettle mixer. The gum is then sent through a series of rollers that forms into a thin, wide ribbon. During this process, gum away from sticking and to enhance the flavour by the light coating of finely powdered sugar or sugar substitutes is added to keep. In a carefully controlled room, minimum upto 48 hrs is need to cooled. This allows the gum to set properly. Finally the gum is cooled at a carefully controlled temperature and humidity. Limitations-Uniformity and accuracy of the drug content is not achieved. Lack of precise form, shape or weight of the dosage form. Theycontain the high moisture content.

2. Cooling, Grinding and Tableting Method (Thermoliable)

This technique has been progressive with an effort to lower the wetness content and ease the difficulties stated in conventional method.

- **Cooling and Grinding (CG) -** The CG composition (base) is cooled to a temperature at which the subsequent grinding step without adhesion to the grinding apparatus

by composition is sufficiently brittle and would remain brittle. The temperature required for cooling and by observing the properties of the cooled chew gum composition by determined in part. Generally the temperature of the refrigerated mixture is around -15oC or lower. Amongst the various coolants and it can be given temperature as low as -78.5c it sublimes readily on warming the mixture is not absorbed by the chewing gum composition does not interact adversely with the processing hazardous by they are like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide is preferred. The refrigerated composition isthen crushed or ground to obtain minute fragments of finely ground pieces of the composition.

➢ **Tableting-** Coolant is removed from the above and all the desired excipients are added to it. A uniform blend is formed in a suitable blender. The mixture is then compressed into tablets. Limitation-it requires equipment other than conventional tableting equipment and requires careful monitoring of humidity during the tableting process.

3. Direct compression method

To overcome the limitations of the above two methods this method is selected. Moreover it is one of the most convenient method of manufacturing medicated chewing gum. It is a simple method. All the ingredients along with the gum base and the drug are mixed properly and triturated for about 15 to 20 minutes to get a homogenous mixture. The blend is then mixed with the lubricants and punched into tablets.

1.2 General Composition of The Medicated Chewing Gum (Mcg).

Table No 1.1: Composition Medicated Chewing Gum.

Active agent	Approximately 50%
Chewing gum base	15-45
Plasticizers	0.5-15
Sweeteners	Up to 60%
Flavouring agents	0.01-1%
Lubricants	0.2-1%
Coloring agent	<0.1%
Adjuvants	Up to 50%

➢ **Active agent-** In medicated chewing gum active pharmacological agent may be present in core or coat or in both. A saliva soluble ingredient will be completely released within 10-15 minutes of chewing whereas lipid soluble ingredient will dissolve in the gum base and thereafter be slowly and completely absorbed.

➢ **Chewing gum base-** it is the base of the medicated chewing gum, mainly classified as natural or synthetic gum base.

➢ **Plasticizer**-these are to regulate cohesiveness of product. They are divided into natural plasticizers and synthetic plasticizers.

➢ **Sweeteners-** Sweeteners are used for soothing taste on tongue, softners to blend the ingredients and retain moisture. They are divided into aqueous sweeteners and bulk sweeteners.

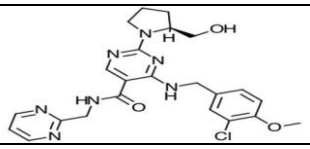
➢ **Colouring agents**-It includes FD and C type dyes and lakes, fruit and vegetable extracts.

➢ **Flavouring agents-** they are used to improve flavour in the medicated chewing gum. It includes mint oil, peppermint oil, etc.

➢ **Lubricants-** Helps the blend from sticking.

1.3. Drug and Polymer Profile

1.3.1 Drug Profile[25]

Name	Avanafil
Iupac name	4-[(3-Chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2- pyrimidinylmethyl)-5-pyrimidinecarboxamide
Category	PHOSPHODIESTERASE 5(PDE 5) INHIBITOR
Molecular Formula	$C_{23}H_{26}ClN_7O_3$
Molecular Weight	483.95
Structure Formula	
Appearance	White Crystalline Powder
Solubility	Water Solubility (0.0297mg/ml)
Half life	5-10 Hours
Oral-Bio Availability	38-41%
Metabolism	Hepatic First Pass Metabolism
Pka	12.53
Log p	2.78
Melting point	163-166°C
Λmax	248nm
Dose	50mg

Mechanism of action	Avanafil inhibits the cGMP specific phosphodiesterase type 5 (PDE5) which are accountable for deprivation of cGMP in the quantity cavernosum located around the penis.(Cyclic GMP causes smooth muscle relaxation and increased blood flow into the corpus cavernosum). The inhibition of phosphodiesterase type 5 (PDE5) by avanafil enhances erectile amount of Cgmp function by increasing the.

AIM, RATIONAL AND OBJECTIVE

1.4 AIM

- Formulation and Evaluation of Medicated Chewinggum of Avanafil.

1.5 RATIONAL

- Avanafil **undergoes first pass hepatic metabolism**. The chewing gum may reduce first pass hepatic metabolism, so it is selected for this formulation.
- Avanafil belong to BCS Class II so has lower solubility and higher permeability, So it appropriate candidate for rapid dissolving chewing gum as it may improve its bioavailability.
- For the better patient compliance.

1.6 OBJECTIVE

- To increase the solubility of drug by preparing Avanafil- β-cyclodextrin (β-CD) inclusioncomplex.
- To formulate and evaluate fast dissolving chewing gum of avanafil.
- To evaluate preformulation characteristics.
- To carry out in-vitro dissolution studies.
- To carry out optimization using different polymer to achieve the fast disintegratingdosage form.
- To carry out stability studies.

1.7 MATERIALS AND METHOD[5,6,7,8,9,10]

1.7.1 List of ingredients

Table 1.2: Ingredients to be used in the formulation.

Category	Name of the Ingredient	Manufacturer
Chewing gum base	Polyvinylacetate	Chemdyes Corporation
Drug	Avanafil	Sunrise Remedies Pvt.Ltd
Sweetener	Sucrose	Chemdyes Corporation
Flavoring agent	Peppermint	Chemdyes Corporation
Plasticizers	Glycerin	Chemdyes Corporation
Adjuvant and Fillers	Calcium Carbonate	Chemdyes Corporation
Dipeptide based sweeteners	Aspartame	Chemdyes Corporation
Water soluble sweetening agents	Mannitol	Chemdyes Corporation
Solubility Enhancer	ß-cyclodextrin (ß-CD)	Astron Chemicals

1.7.2. List of Equipments

Table 1.3: Equipments to be used in the formulation.

EQUIPMENT	COMPANY	MODEL NO.
UV-Visible Spectroscopy	Shimadzu	UV-1800
Digital Balance	Swisser Instruments, Gandhinagar	C-100859
Dissolution Test Apparatus	Fabricated instrument	-
Hardness Tester	EIE Instrument Pvt.Ltd Ahmedabad	-
FTIR	Sicart Research Lab	Spectrum GX
DSC	Shimadzu	DSC-60

METHOD

1.8 Preformulation Studies

Preformulation study was carried out which focuses on prefound understanding of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage forms, first Preformulation studies were performed. Various Preformulation studies which were carried out are discussed in following sections.

Identification of Drug

1.8.1 Determination of Melting point

Melting point of Avanafil was determined by capillary method.

METHOD

In this method the capillary tube was sealed with gentle heating from one end. Then the small quantity of drug Avanafil was filled into the sealed capillary. Capillary was tied to the tube (thermometer) containing the oil phase in such a way that the sealed part of the capillary containing Avanafil was dipped into the oil. Gently the oil bath was heated. Assoon as the powder starts melting, the heating was stopped and the temperature was noted down.

Melting point of Avanafil was found to be 163-167^{o}C which is in the range of the reported melting point 163-166^{o}C.

1.8.2 By UV spectrophotometry

UV-Visible Spectrophotometric method Standard curve for Avanafil

Standard curve of Avanafil was taken in pH 6.8 Phosphate buffer as a medium.

Preparation of pH 6.8 phosphate buffer

28.8 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate was weighed and diluted upto 1000 ml to get pH 6.8 phosphate buffer.

Preparation of standard stock solution of Avanafil in phosphate buffer pH 6.8

Standard drug solution of Avanafil was prepared by dissolving (10 mg) Avanafil in 100 ml of pH 6.8 phosphate buffer to obtain standard stock solution (100 µg/ml) concentration.

Determination of UV absorption maxima

For the determination of λmax, 10 µg/ml of Avanafil solution was prepared from standard stock solution with pH 6.8 phosphate buffer. Spectrum was scanned between 200-400nm UV-spectrophotometer and the suitable absorption maxima was selected

Preparation of Working Solution for standard curve of Avanafil

From the prepared stock solution (100 µg/ml), accurately measured standard working sample solution of avanafil (1,2,4,6,8 ml) were taken in series and transfer to 10 ml of volumetric flask and diluted upto the mark with pH 6.8 phosphate buffer to prepare the concentration of 10,12,14,16,18 µg/ml.

The absorbance of prepared solution of Avanafil in pH 6.8 phosphate buffer was measured at 247nm using UV–visible Spectrophotometer against pH 6.8 phosphate buffer as blank and calibration curve of absorbance v/s concentration was plotted.

1.8.3 Identification by FTIR (Fourier Transform Infra-Red Spectroscopy)

FTIR Spectroscopy was carried out for the identification of Avanafil. FTIR spectrum of the obtained sample of drug is compared with standard functional group frequencies of Avanafil. A Pellet of the drug & KBr was prepared using hydraulic pellet press at a pressure of 7-10tones. FTIR was scanned from 400-4000 cm^{-1}.

1.8.4 By DSC

Avanafil showed sharp endothermic peak that corresponds to it's melting point 163-166^{0}C.

1.8.5 Drug – excipients compatibility study by FT-IR

- Drug (Avanafil) + Polyvinylacetate
- Drug (Avanafil) +Glycerine
- Drug (Avanafil) + Beta-Cyclodextrin
- Drug (Avanafil) + Polyvinylacetate + Glycerine + Sucrose + Peppermint + Calcium carbonate + Aspartame + Mannitol + Beta-Cyclodextrin

Solubility study

10 mg of Avanafil was taken and solubility in distilled water, 6.8 N PHOSPHATE solution, methanol,6.8 phosphate buffer was carried out by analyzing in UV visible spectroscopy 247nm.

1.9 Method For Increasing The Solubility of Avanafil[11]

Solubility of Avanafil is increased by preparing its inclusion complex using ß-cyclodextrin (ß-CD)

The inclusion complex of drug with ß-CD was prepare by wetting the mixture of Avanafil: ß-CD in the different molar ratios 1:0.5,1:1,1:2 in mortar with a small volume of water – methanol (1:1 v/v) solution. The thick slurry that formed was kneaded for 45 min and then dried at 45 °C. The dried mass was sieved through sieve no. 60. And Store in a desiccator till further use.

Table 1.4: Different ratios of Drug- ß-CD for preparation of inclusion complex Characterization of Avanafil : β-cyclodextrin inclusion complex.

Inclusion complex composition	Drug- ß-CD ratio	Formulation code
Avanafil: ß-CD ratio	1:0.5	C1
	1:1	C2
	1:2	C3

1.9.1 Solubility determination of Drug:β-cyclodextrin inclusion complex

10 mg sample was taken in 10ml of 6.8 phosphate buffer

Agitated at 37 ^{0}C for 24 hours

Sample was filtered through 45 µm filter paper and diluted.

Content is measured in UV spectroscopy at 247 nm.

1.9.2 Drug content estimation

In 100 ml volumetric flask an accurately weighed quantity of inclusion complex equivalent to 10 mg of drug was taken and dissolved in small Quantity of pH 6.8 phosphate buffer and make up the volume with it. This gives the concentration of 100 µg/ml.

From above solution 1 ml was taken and further diluted to 10 ml with pH 6.8 Phosphate buffer this gives the concentration of 10 µg/ml.

This solution was then assayed for drug content using UV-Visible spectrophotometer at 247nm. And drug content was estimated of the prepared inclusion complex.

1.9.3. Characterization of Avanafil inclusion complex

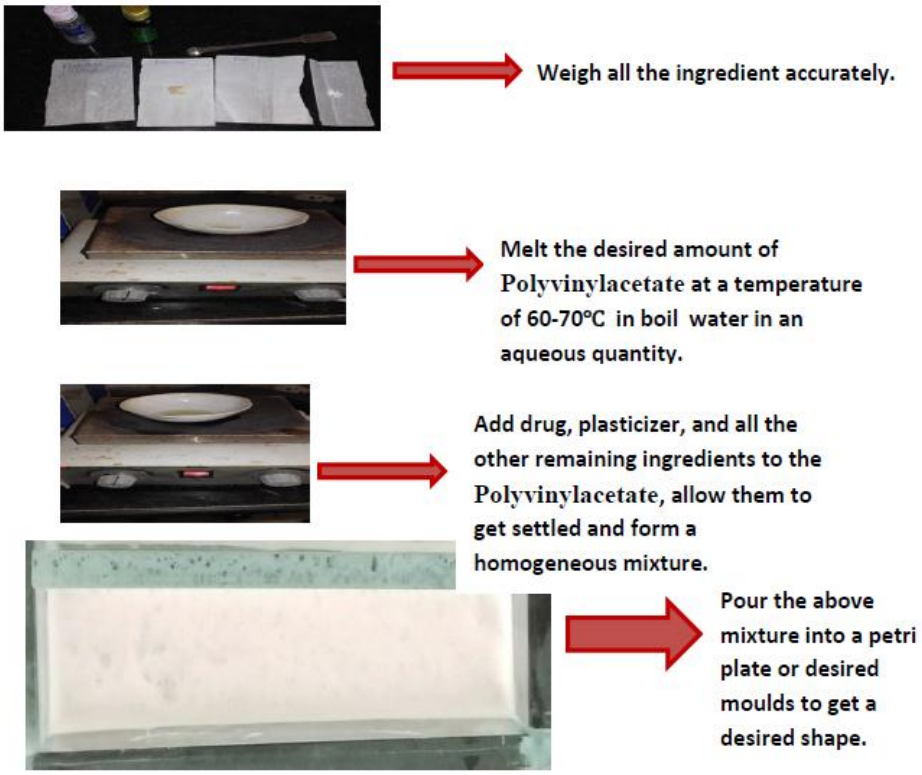
An accurately weighed quantity of inclusion complex

equivalent to 10 mg of drug was taken into 100 ml volumetric flask and dissolved in small Quantity of pH 6.8 Phosphate buffer and make up the volume with it. This gives the concentration of 100 µg/ml.

From above solution 1 ml was taken and further diluted to 10 ml with pH 6.8 Phosphate buffer this gives the concentration of 10 µg/ml.

This solution was then assayed for drug content using UV-Visible spectrophotometer at 247nm. And drug content was estimated of the prepared inclusion complex.

Method of Preparation of Mcg



Method of preparation of medicated chewing gum

2.1 Method Of Preparartion of Medicated Chewing Gum

- Weigh all the ingredients accurately.
- Melt the desired amount of Polyvinylacetate at a temperature of 60-70℃ in to the boil water. Add drug, plasticizer, and all the other remaining ingredients to the Polyvinylacetate, allow them to get settled and form a fine mixture.
- Pour the above mixture into a petri plate or desired moulds to get a desired shape.

2.1.1. Evaluation parameters

- **Drug content-** Randomly selected MCG was crushed in phosphate buffer of pH 6.8 in mortar with pestle, solution was then withdrawn and absorbance was measured. The values thus were substituted into **A= abc**, where.

A= Absorbancea= Absorptivity.
b= Centimetre of the test tube.
c= concentration.

- **Drug release**- Randomly selected MCG was kept in a modified disintegrating test apparatus, the apparatus was filled by the phosphate buffer of pH 6.8. Stroke speed of 60 strokes per minute was adjusted; 1ml of the sample was withdrawn every 5 minutes which was replaced by the fresh phosphate buffer of pH 6.8. Absorbance of the withdrawn buffer was taken. %Cumulative index was calculated from it. This value gave the drug release rate.

% Cumulative index= (1-(absorbance (t)/absorbance (t_0))*100)

Where, absorbance (t) = absorbance at initial time absorbance (t_0) = absorbance at final time.

- **Organoleptic properties-** Such as colour, odour, surface texture and appearance were checked out.
- **Short term stability studies** were done according to the ICH guidelines. The selected formulation was packed and sealed in aluminium packaging coated inside with polyethylene. Accelerated stability studies carried out at 40 °C±2 °C/75% RH±5% RH
- **Stickiness:** The formulated medicated chewing gum base was placed on plain surface A mass of 250 gm was hammered on it upto 10 min. The frequency of hammering was about 30 min. None of the batch

stuck to hammer or surface.

- **Weight variation:** Chewing gum from each batch were individually weighed on analytical balance, the average weight and standard deviation were calculated which was found in acceptable limit.
- **Plasticity/hardness:** Hardness of chewing gum was determined by Monsanto hardness tester and the average hardness and standard deviation were reported.
- **Percentage drug content:** % drug content of formulated chewing gum was determined by weighing 1000 mg chewing gum equivalent to 10 mg Chlorhexidine gluconate and transferring into volumetric flask. About 60 ml of artificial saliva was added, sonicated for 10 min, then shaken by mechanical means for 30 min and volume was adjusted to 100 ml with the same solvent. Again it was sonicated and filtered. Percentage drug content was determined spectrophotometrically at 231 nm. Same procedure was repeatedfor three times.

2.1 Preparation of the preliminary batches.

2.1.2 Preparation of the preliminary batches.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Inclusion complex	100	100	100	100	100	100	100	100	100
Polyvinylacetate	210	210	210	245	245	245	280	280	280
Glycerin	10	15	20	10	15	20	10	15	20
Sucrose	200	200	200	200	200	200	200	200	200
Calcium carbonate	30	30	30	30	30	30	30	30	30
Aspartame	3	3	3	3	3	3	3	3	3
Manitol	145	140	135	110	105	100	75	70	65
Peppermint flavour	2	2	2	2	2	2	2	2	2

2.1.3 Short time stability study[3,12,13]

Drug decomposition or degradation happens during storage, due to chemical modification of the API or owing to product instability, lower the amount of the drug in the dosage form. The capacity of a scrupulous API or dosage form in a definite container to remain inside its physical, chemical, therapeutic, and toxicological specifications is known as Stability. The formulation is quite stable at different conditions of storage is known by stability study. Accelerated stability studies conceded at 40 °C±2 °C/75% RH±5% RH for 1 month.

2.1.4. Stability Studies

Drug decomposition or degradation happens during storage, due to chemical modification of the API or owing to product instability, lower the amount of the drug in the dosage form. The capacity of a scrupulous API or dosage form in a definite container to remain inside its physical, chemical, therapeutic, and toxicological specifications is known as Stability. The formulation is quite stable at different conditions of storage is known by stability study. The accelerated stability studies were carried out on the most satisfactory formulation (Batch) as per ICH guidelines Q1C.The selected formulation F was evaluated for accelerated stability studies at 40±2°C / 75±5% RH conditions for 1 month using stability chamber. At the end of studies, sample was analyzed for drug content, % drug release, organoleptic properties. Dissolution profile was shown in the Figure and it was found almost same drug release profile in both the cases. The data, after stability period of evaluation parameters were found nearly same as it was before the stability period. Hence stability study indicates that the formulation is quiet stable at accelerated conditions. After storage at 40±2°C / 75±5% RH. So, it was clear that drug was thermally stable as well as not affected by high humidity at 40±2°C / 75±5% RH.

2.1.5. In vitro buccal permeation study for released drug[14,15,16]

In an in vitro Franz diffusion Buccal permeation study, average proportion of AVANAFIL which was released from optimized formulation after 30 min of chewing 60.73% were permeated which was placed in the donor compartment of diffusion cell containing phosphate buffer of salivary pH. It was allowed to permeate through buccal mucosa for 30min. After 30min (which is normal average chewing time), the sample was collected from the receiver compartment and analyzed by the UV-spectrophotometer at 247nm, to determine the total content of AVANAFIL permeated through buccal mucosa.

Figure 1

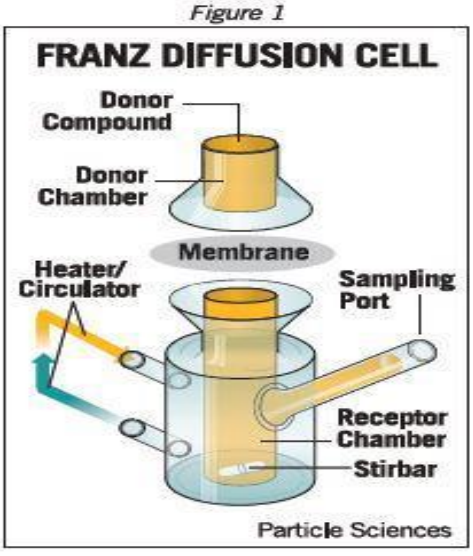


Fig. 1.4: Franz diffusion Cell.

3.0 RESULTS AND DISCUSSIONS

3.1. Preformulation studies and evaluation results

3.1.1 Identification of drug

3.1.2. Melting point determination

Table 3.1: Melting point study.

Drug	Standard value	Observed value
AVANAFIL	163 - 166^{0}C	163– 167^{0}C

Fig. 1.5: Melting point apparatus.

3.1.3 By UV spectrophotometry

Determination of absorption maxima (λmax) of Avanafil in pH 6.8 Phosphate buffer. The solution containing 10 µg/ml concentration of Avanafil was prepared from standard stock solution, then UV Scan was taken between the wavelength 200-400nm.It gave a peak at247nm and it was selected as λmax for Avanafil Which is shown in figure 6.3.

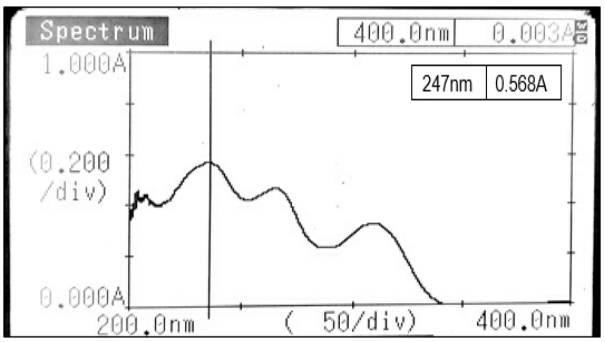


Fig. 1.6: UV curve for pure Avanafil.

Calibration Curve of Avanafil in pH 6.8 Phosphate buffer

Standard calibration curve of Avanafil was drawn by plotting absorbance v/s concentration. The λmax of Avanafil in pH 6.8 phosphate buffer was determined to be 247nm, So absorbance are taken at 247nm. The absorbance value are reported. Standard calibration curve of Avanafil. Table 9.1.3: Absorbance of Avanafil in pH 6.8 phosphate buffer at 247nm.

Tab. 3.2: Concentration vs. Absorbance.

Concentration	Absorbance
0	0
2	0.142
4	0.223
6	0.321
8	0.432
10	0.561
12	0.649
14	0.737
16	0.859
18	0.943

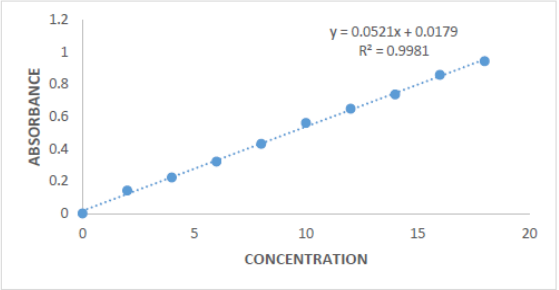


Figure 1.7: Standard calibration curve for Avanafil.

By FT-IR spectra

3.1.4. Identification of drug (Avanafil) by FTIR spectroscopy

For identification of drug, Avanafil (pure drug) IR Spectra was compared to standard IR Spectra of Avanafil, It indicated that functional group frequencies of sample drug were in range of the reported range which indicates that the obtain sample was Avanafil and was pure. The major peaks obtained in the FTIR spectra of Avanafil were found to be correlating with the functional group present in the structure of the drug. The result of FTIR study along with the interpretation are shown in figure 3.1 and table 3.2.

Drug (Avanafil)

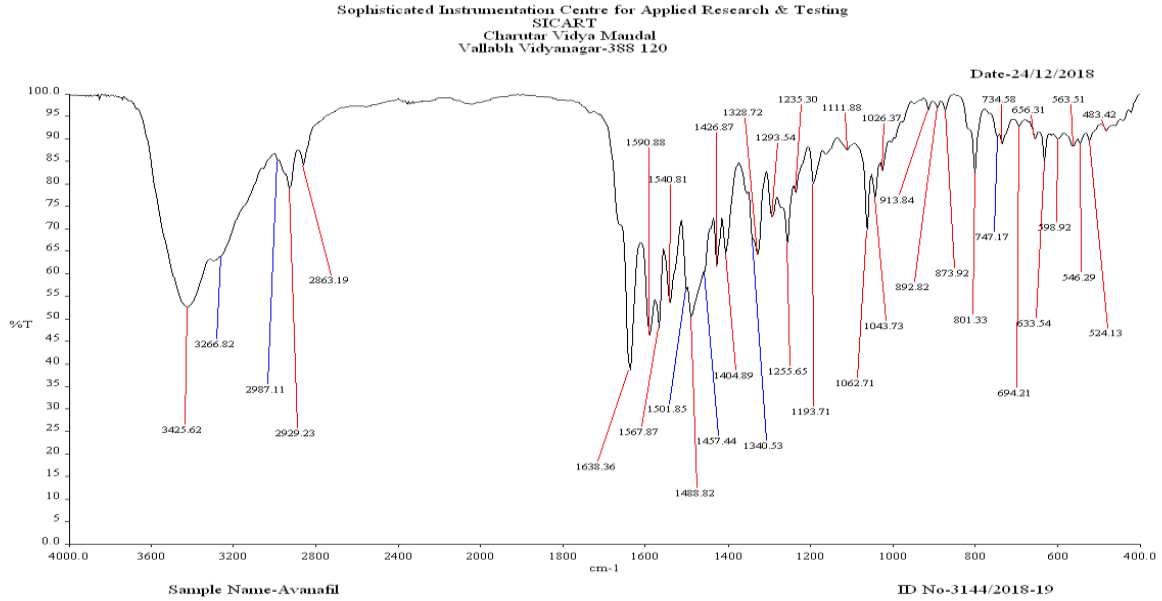


Figure 3.1: FTIR Spectra of Avanafil.

Table 3.1.1: Result of FTIR Study of AvanafilDrug – excipient compatibility study.

Functional Groups standard Frequency(cm^{-1})	Observed Frequency (cm^{-1})	Interpretation
C=O stretching of amide (1600-1900)	1638.36	The drug sample wasfound to be Avanafil
O-H (3000-3700)	3425.62	
-N=N (1500-1700)	1567.87	
-C-CL (600-800)	694.21	

Fourier Transform Infra-Red (FT-IR) Specroscopy

Compatibility study war performed using FT-IR Spectrophotometer. The IR spectra of physical mixture of drug and polymer was studied by making KBr pallet and it was compared with the pure drug spectra. The peaks obtained in the spectra of physical mixture correlates with spectra of pure drug, which indicates that the drug is compatible with the formulation component.

Drug (Avanafil) + Polyvinylacetate

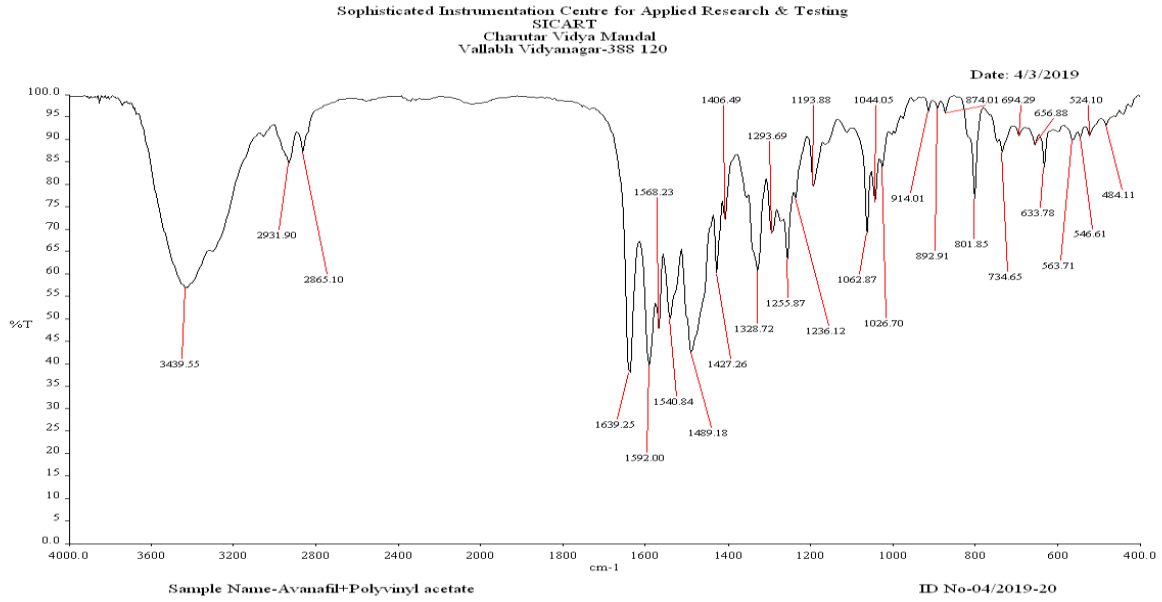
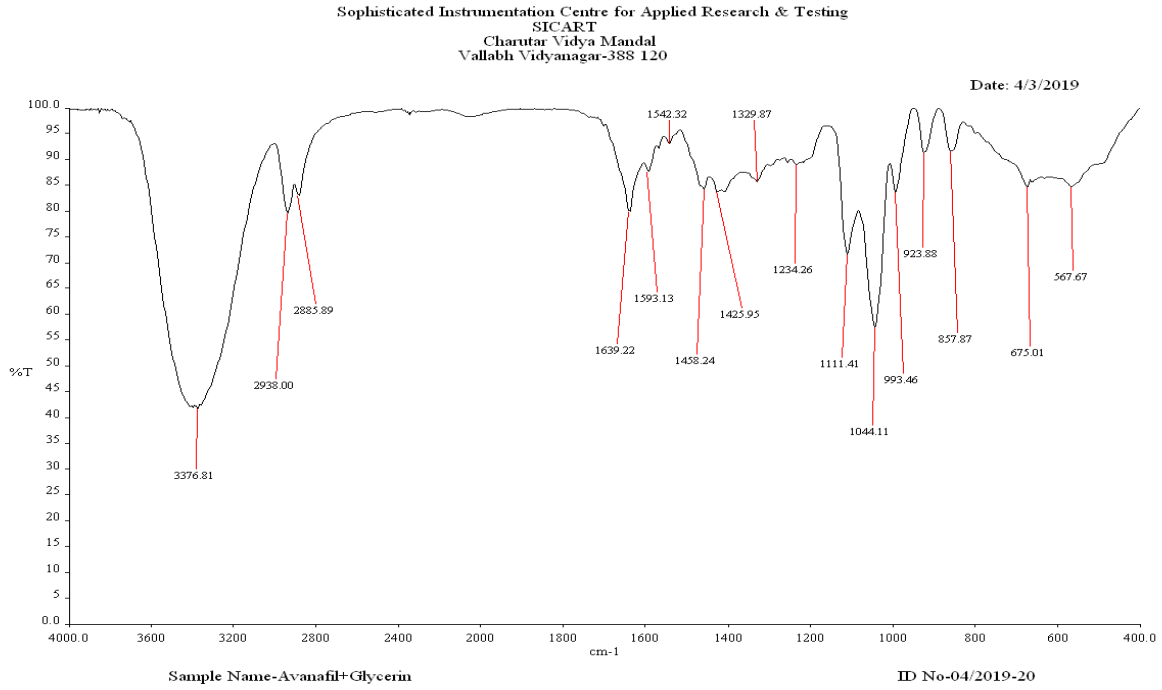
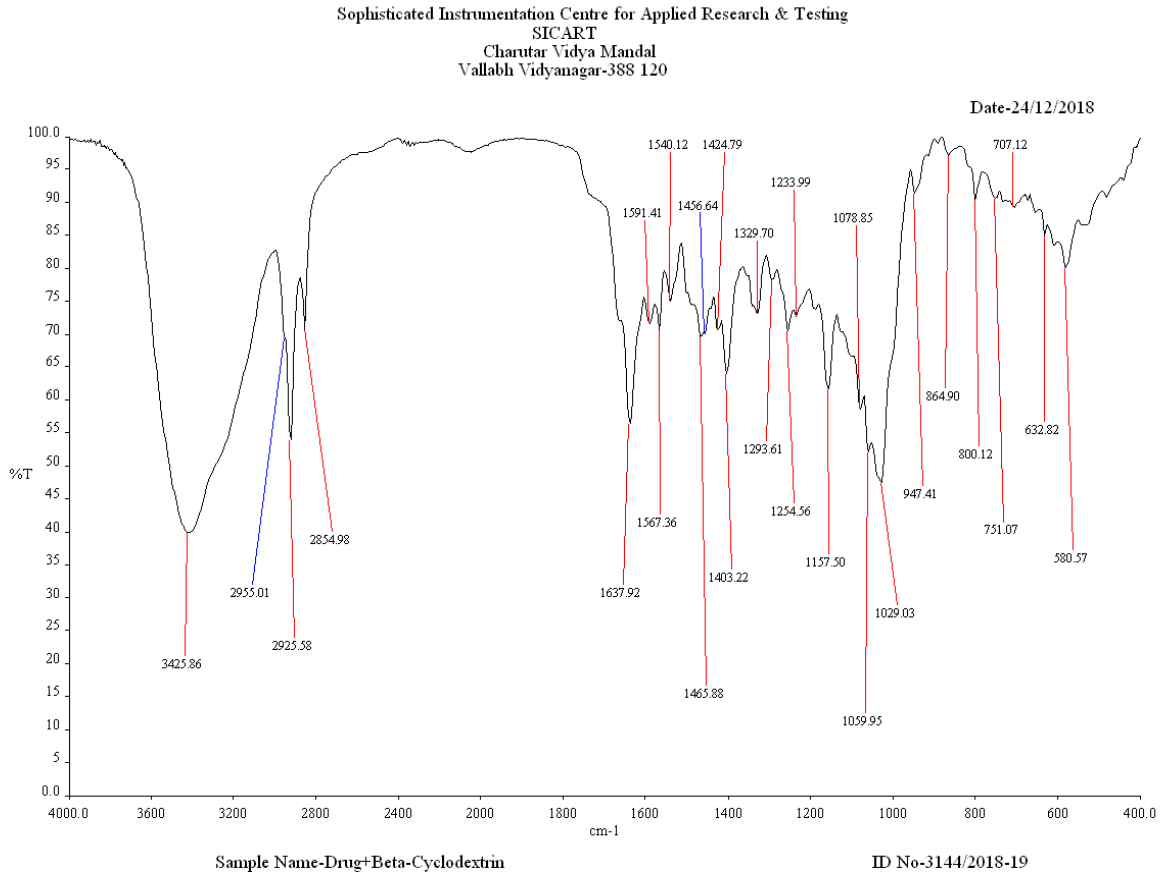


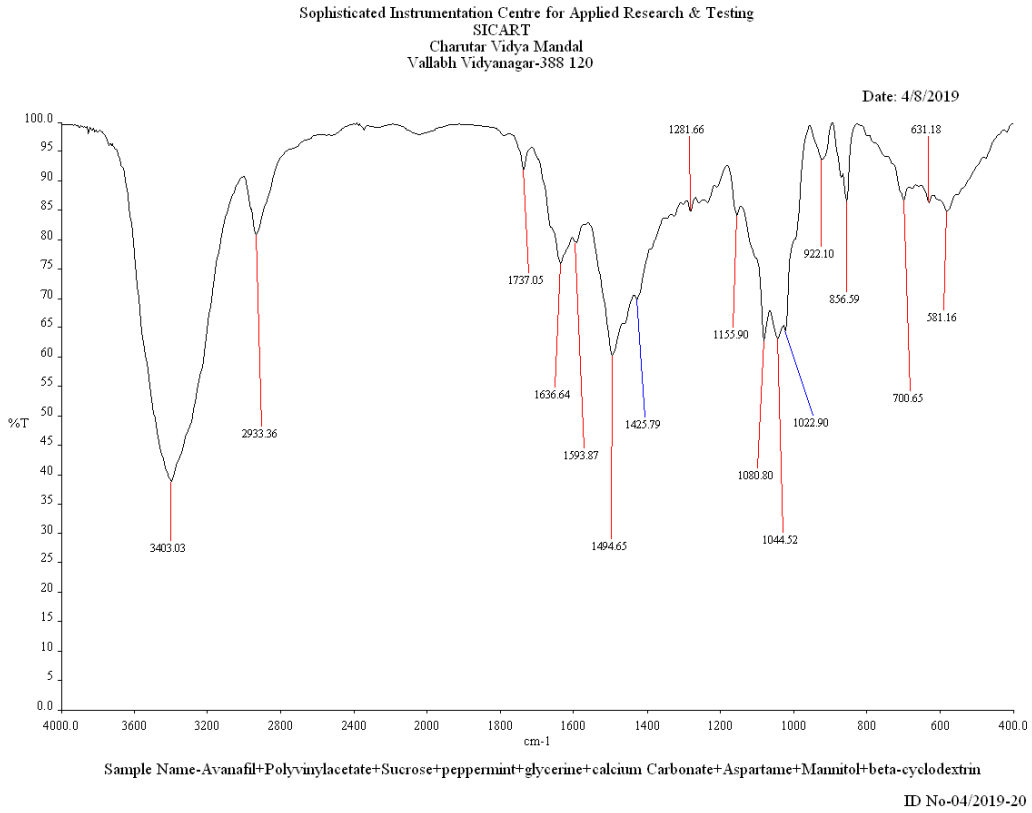
Figure 3.2: Drug-Polymer Compatibility Study.



3.3. Drug (Avanafil) + Glycerin.



3.4. Drug (Avanafil) + Beta-Cyclodextrin



3.5. Drug (Avanafil) + Polyvinylacetate + Glycerine + Sucrose + Peppermint + Calcium Carbonate + Aspartame + Mannitol + Beta-Cyclodextrin

Table 3.6: Compatibility study of Avanafil with other polymer.
Table 3.6: Result of Drug-Polymer Compatibility Study.

Functional Group	Avanafil	Avanafil + Polyvinylacetate	Avanafil + Glycerin	Avanafil + Beta-Cyclodextrin	Avanafil + Polyvinylacetate + Glycerin + Sucrose + Calcium Carbonate + Aspartame + Mannitol + Peppermint+ Beta-Cyclodextrin	Interpretation
C=O (1600-1900)	1638.36	1639.25	1639.22	1637.92	1638.02	There is no interaction found between drug and polymer
O-H (3000-3700)	3425.62	3439.55	3376.81	3425.86	3423.36	
-N=N (1500-1700)	1567.87	1592.00	1593.13	1637.92	1591.19	
-C-Cl (600-800)	694.21	734.65	675.01	751.07	755.23	

Interpretation
As seen in the Table, all peaks is nearby with peak of pure drug. So there is no interaction between drug and polymer.

3.1.5. Identification of drug (Avanafil) by DSC

3.1.6. The DSC thermogram of Avanafil showed sharp endothermic peak at 165.78^{0}C that corresponds to its melting point 163-166 ^{0}C Shown in Figure 9.1.8

Avanafil showed sharp endothermic peak that corresponds to it's melting point 163-166 ^{0}C.

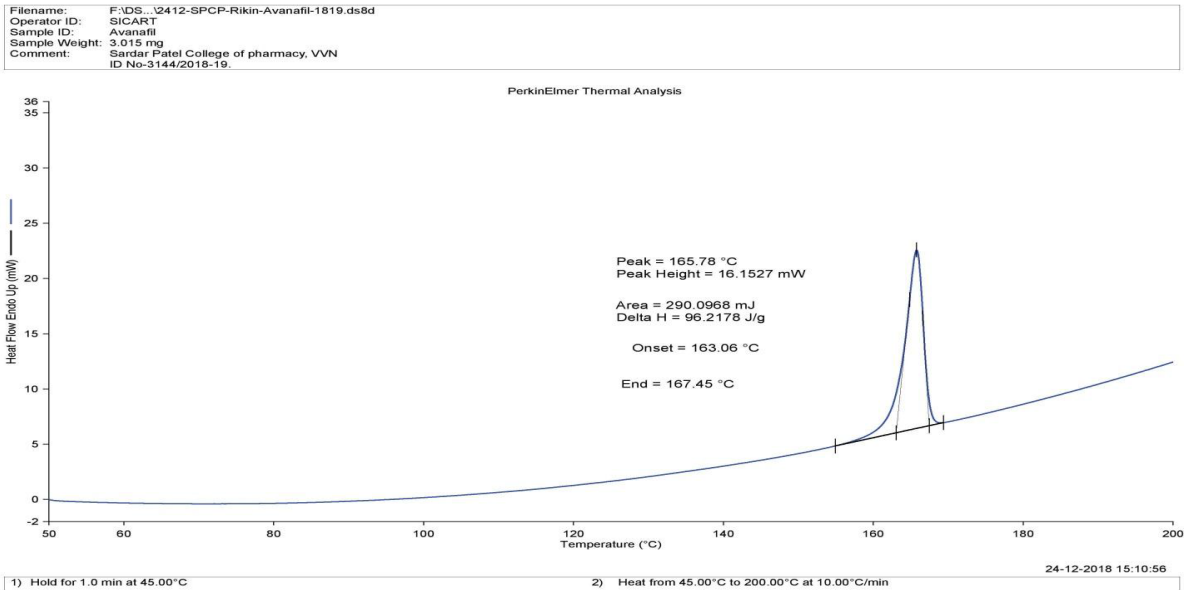


Figure 3.7: DCS Thermogram.

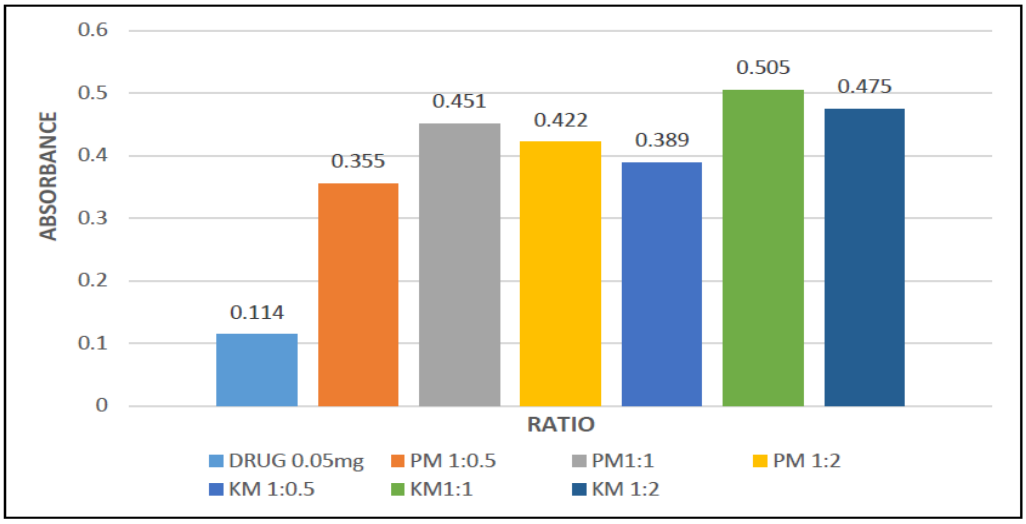
4.0. Characterization of Avanafil: ß-cyclodextrin (ß-CD) inclusion complex

4.1.1. Solubility determination of Avanafil and Avanafil: β-cyclodextrin inclusion complex in Simulated saliva of pH 6.8 Buffer

Solubility of Avanafil: ß-cyclodextrin inclusion complex was checked by taking 10mginclusion complex in 10 ml of pH 6.8 phosphate buffer it was agitated at 37^{O}C for 24 hours and after filtration content was measured in UV spectrophotometer at 247nm results are shown in table.

Table 4.1: Solubility determination of Avanafil and Avanafil : β-cyclodextrin inclusion complex in Simulated saliva of pH 6.8 Buffer.

Formulation ratio Drug: β-cyclodextrin	Solubility ((µg/ml)	Increase in the number offolds
Drug	35.30	-
PM 1:0.5	65.38	1.85
PM 1:1	83.63	1.27
PM 1:2	78.11	2.21
KM 1:0.5	71.84	2.03
KM 1:1	93.89	2.65
KM 1:2	88.19	2.49



KM - Kneading method and **PM** - Physical mixture

Figure 4.2: Solubility of Avanafil inclusion complex.

4.1.2. Theoretical yield, Practical yield and Powder yield (%) of Avanafil inclusioncomplex.

Formulation	Theoretical yield(mg)	Practical yield(mg)	Powder yield(%)
1:0.5	750	690.9	92.12±0.56
1:1	1000	955.5	95.55±1.59
1:2	1500	1406.1	93.74±0.07

4.1.3. Solubility of drug

Table 10.1.4 Solubility of drug4.3: Solubility of Avanafil inclusion complex.

SR NO	Solvent	ml ofsolvent required (10 ml)	Solubility % (µg/ml)
1	Distilled water	10 ml	64(6.4 µg/ml)
2	6.8 N PHOSPHATE buffer	10 ml	68(6.8 µg/ml)
3	Methanol	10 ml	97(9.7 µg/ml)
4	Chloroform	10 ml	96(9.6 µg/ml)

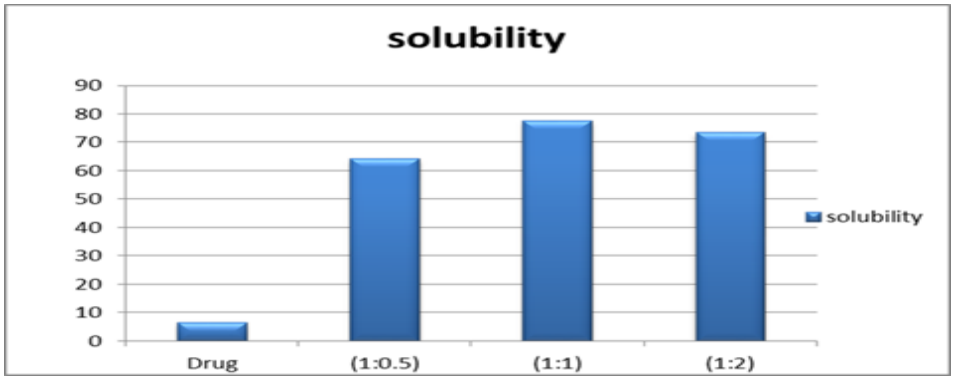


Table 4.4 Drug content of Avanafil inclusion complex and Powder yield %.

Formulation	Drug Content (%)	Powder yield (%)
1:0.5	86.45±0.75	92.12±0.56 (9.21 mg)
1:1	90.5±0.42	95.55±1.59 (9.55 mg)
1:2	88.11±0.473	93.74±1.59 (9.37 mg)

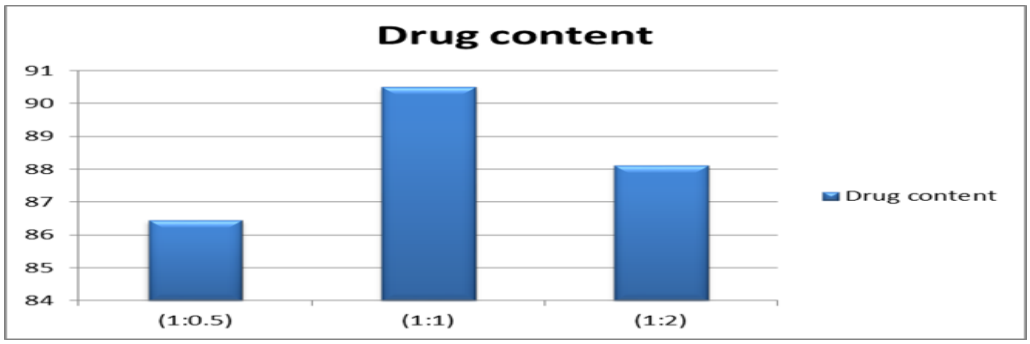


Figure 4.5 Drug content of Avanafil inclusion complex

4.1.4..Pre-Evaluation parameter

Table 4.6: Pre-Evaluation parameter

SR NO	Batch	Stickiness	Colour	Appearance
1	F1	Non sticky	Off white-light yellow	Soft
2	F2	Non sticky	Off white-light yellow	Soft
3	F3	Non sticky	Off white-light yellow	Soft
4	F4	Non sticky	Off white-light yellow	Hard
5	F5	Non sticky	Off white-light yellow	Soft
6	F6	Non sticky	Off white-light yellow	Soft
7	F7	Non sticky	Off white-light yellow	Hard
8	F8	Non sticky	Off white-light yellow	Soft
9	F9	Non sticky	Off white-light yellow	Soft

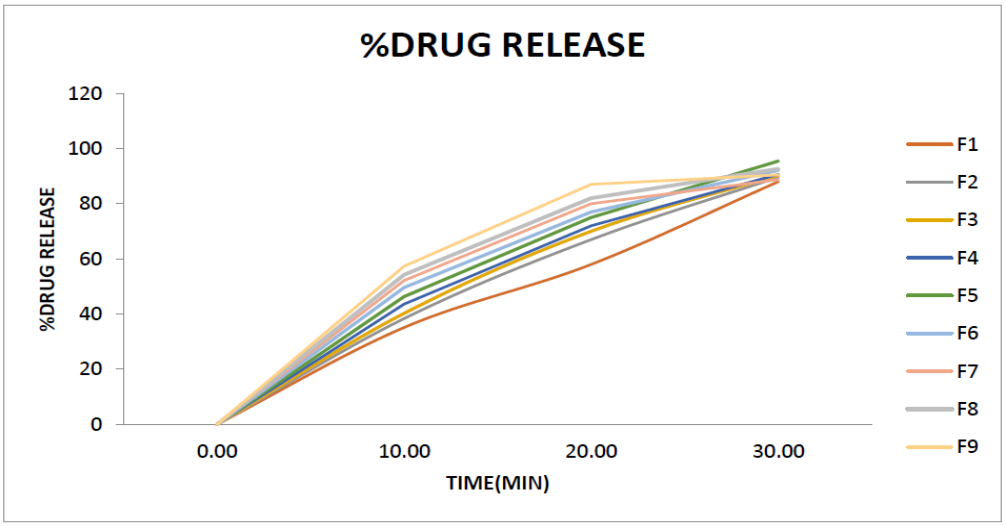
4.1.5. Post-Evaluation parameter

SRNO	Batch	Weight variation (mg)	HardnessKg/cm^2	% drug content	% drug release
1	F1	700.2±0.21	2.5±0.1	94.01 %	92.81 %
2	F2	700.5±0.44	2.5±0.1	96.03 %	94.28 %
3	F3	700.6±0.31	2±0.1	92.05 %	91.18 %
4	F4	700.4±0.64	2.5±0.1	95.08 %	93.36 %
5	F5	701.6±0.14	2.5±0.2	97.07 %	95.45 %
6	F6	700.2±0.52	2.5±0.1	93.05 %	92.14 %
7	F7	700.9±0.25	2±0.12	90.06 %	88.76 %
8	F8	700.4±0.32	2.5±0.1	93.09 %	92.63 %
9	F9	700.9±0.34	2±0.1	91.06 %	90.52 %

4.1.6. Post Evaluation parameters of % Drug release

Table 4.7: Post Evaluation parameters of % Drug release.

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
0 min	0 %	0%	0%	0%	0%	0%	0%	0%	0%
10 min	35.13±0.12	38.36±0.28	40.25±0.39	43.62±0.28	46.32±0.9	49.63±0.2	52.13±0.3	54.21±0.45	57.31±0.8
20 min	58±0.12	67±0.23	70±0.8	72±0.7	75±0.7	77±07	80±0.47	82±0.21	87±0.31
30 min	92.81±0.32	94.28±0.87	91.18±0.78	93.36±0.45	95.45±0.21	92.14±0.45	88.76±0.45	92.63±0.24	90.52±0.45



Dissolution apparatus by fabricated method

Fig 4.8: Medicated chewing of batches from F1-F9.

Fig 4.9: Medicated chewing gum of batch F5.

5.0 STABILITY STUDIES

Drug decomposition or degradation happens during storage, due to chemical modification of the API or owing to product instability, lower the amount of the drug in the dosage form. The capacity of a scrupulous API or dosage form in a definite container to remain inside its physical, chemical, therapeutic, and toxicological specifications is known as Stability. The formulation is quite stable at different conditions of storage is known by stability study. The accelerated stability studies were carried out on the most satisfactory formulation (Batch) as per ICH guidelines Q1C.The selected formulation F was evaluated for accelerated stability studies at 40±2°C / 75±5% RH conditions for 1 month using stability chamber. At the end of studies, sample was analyzed for drug content, % drug release, Organoleptic properties. Dissolution profile was shown in the Figure and it was found almost same drug release profile in both the cases. The data, after stability period of evaluation parameters were found nearly same as it was before the stability period. Hence stability study indicates that the formulation is quiet stable at accelerated conditions. After storage at 40±2°C / 75±5% RH. So, it was clear that drug was thermally stable as well as not affected by high humidity at 40±2°C / 75±5% RH.

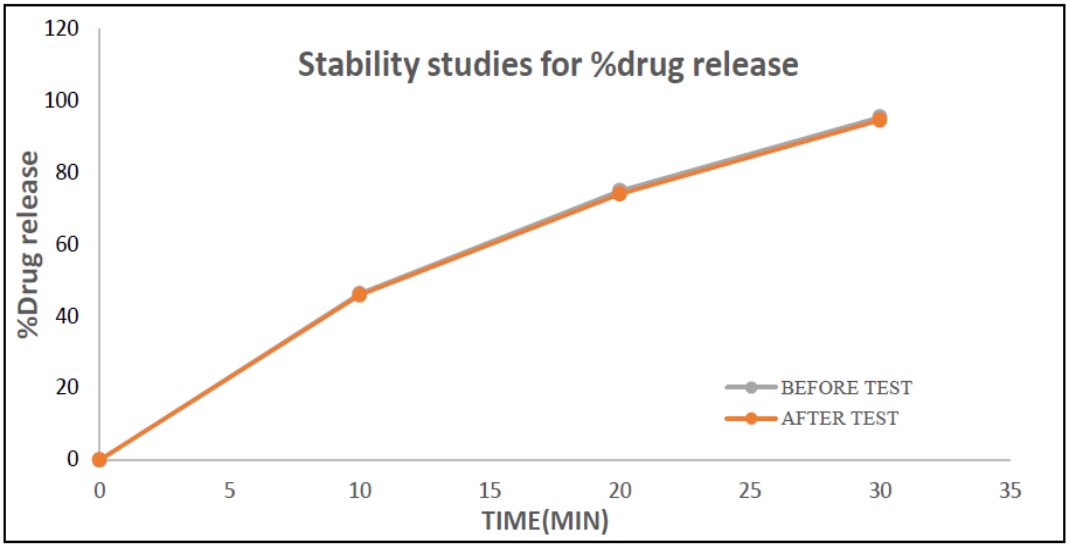
Tab 4.10: Result of Stability Study

Parameter	Before Test	After Test
% Drug Content	97.07 %	96.86 %
% Drug release	95.45 %	94.60%
Organoleptic Properties	Elegant	Elegant

Tab 4.11. Result of % Drug release of stability Study.

Time (min)	Before Test (%)	After Test (%)
0	00	00
10	46.32±0.9	45.90±0.6
20	75±0.7	74±0.5
30	95.45±0.21	94.60±0.30

All data are shown in mean±SD (n=3)

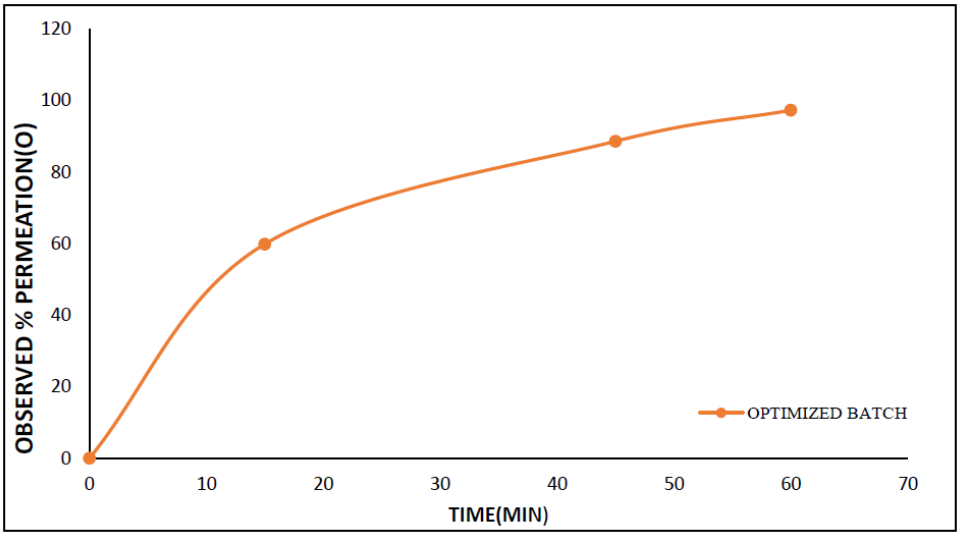


% Drug release of stability Study

In vitro Buccal permeation study for released drug

Tabel 4.12: Result of Buccal permeation study.

Time (min)	Observed % permeation (o)
0	00
10	45.37 %
20	53.055 %
30	60.73 %



Time (min) vs Observed % Permeation (o)

6.0 SUMMARY

Medicated chewing gum of Avanafil was decided to be formulated, so as to overcome the drawbacks of Avanafil such as low bioavailability, improper absorption etc.

With a deep literature survey method of preparation, excipients and evaluation parameters were decide. Melting method was used here for the formulation of the medicated chewingalong with Polyvinylacetate, Sucrose, Peppermint flavour, Glycerin, Calcium Carbonate, Aspartame, Mannitol, ß-cyclodextrin (ß-CD). Evaluation parameters of % drug content, % drug release, organoleptic properties short term stability studies and buccal permeation studies were performed. The results were all satisfactory.

7.0 CONCLUSION

The overall research suggests that medicated chewing gum of Avanafil is a very good idea of formulation. The optimized batch was formulated which gave the desired results, % drug content was 97.07 % and % drug release was 95.45%. It may improve patient compliance, may show fast onset of action, may show good absorption and increased bioavailability.

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