FORMULATION DEVELOPMENT AND EVALUATION OF TADALAFIL ORAL JELLY COMPARATIVE WITH MARKETED PRODUCT

A Dissertation submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY
Chennai-600032

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY
IN
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Under the Guidance of

R. NATARAJAN. M.Pharm., (Ph.D)

DEPARTMENT OF PHARMACEUTICS

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

ELAYAMPALAYAM

TIRUCHENGODE-637205

TAMILNADU.

April-2014

CERTIFICATE

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY
Elayampalaym, Tiruchengode, 637205
Namakkal (DT), Tamilnadu.
Phone: 04288-2344178lines)
Fax: 04288-234417

Dr. N.N.RAJENDRAN. M.Pharm., Ph.D.,
Principal

CERTIFICATE

This is to certify that the Dissertation entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF TADALAFIL ORAL JELLY COMPARATIVE WITH MARKETED PRODUCT"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, is a bonafide project work of **Reg No: 261210605,** in the Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy, Tiruchengode for the partial fulfillment for the degree of Master of Pharmacy under the guidance of **R. NATARAJAN. M.Pharm., (Ph.D)** Swamy Vivekanandha College of Pharmacy, Tiruchengode.

Signature of Principal of P.G. studies
Dr. N.N.RAJENDRAN. M.Pharm., Ph.D.,

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY
Elayampalaym, Tiruchengode, 637205
Namakkal (DT), Tamilnadu.
Phone: 04288-2344178lines)
Fax: 04288-234417

Dr. N.N.RAJENDRAN. M.Pharm., Ph.D.,
Director of P.G Studies and Research.

CERTIFICATE

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Signature of Director of P.G. studies
Dr. N.N.RAJENDRAN. M.Pharm., Ph.D.,

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY
Elayampalaym, Tiruchengode, 637205
Namakkal (DT), Tamilnadu.
Phone: 04288-234417(8lines)
Fax: 04288-234417

R. NATARAJAN. M.Pharm., (Ph.D)
Head, Department of Pharmaceutics

CERTIFICATE

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This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

Signature of the Guide
R. NATARAJAN. M.Pharm., (Ph.D)

DEDICATED TO MY PARENTS, BROTHER AND FRIENDS.....

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C. PRABHU

(Reg No: 261210605

CONTENTS

1. ABSTRACT

The present study aimed to develop a immediate release of tadalafil oral jellies for the treatment of erectile dysfunction. The jellies were prepared by using carbopol 940 with different concentration as a polymer and propylene glycol as a co-polymer. The prepared jellies were evaluated for its various physio-chemical parameters such as pH, appearance, viscosity, in vitro drug release. The obtained result to form physio-chemical parameters complies with standard the in vitro drug release so highest percentage immediate limit release with increased concentration carbopol 940 (F5) this present studies concluded that tadalafil oral jellies alternative dosage for oral dispersible tablets and drug could produce improved bioavailability and compared to other fast releasing dosage form.

2. INTRODUCTION

Erectile dysfunction (ED) is the most common sexual problem in men[1]. ED is defined as a difficulty in initiating or maintaining penile erection adequate for sexual activity. ED has a weighty effect on intimate relationships, quality of life, and overall self-esteem for men. In addition, ED may also be an early indication of undetected cardiovascular disease.One of the largest current studies of ED, Male Aging Study, established that the prevalence of ED increases with age as it affects up to half of the male population between 40 and 70 years old. Thus, as the world's older population increases, it is estimated that the prevalence of ED will double from 152 million men in 1995 to 322 million men in 2025, indicating a dire need to reevaluate current ED therapeutic strategies. In most documented cases, ED may also present with comorbidities of hypertension, diabetes mellitus, obesity, and atherosclerosis.[2]

During the 1980s, most of the pioneering research in ED was sparked by the introduction of intracavernosal vasoactive drugs, which were very effective as agents inducing penile rigidity.It was not until the late 1990's and early 2000's that oral phosphodiesterase-5 inhibitors were introduced, which were truly instrumental in revolutionizing the sexual medicine field. Currently Erectile dysfunction (ED) is treated with PDE5 inhibitors, lodenafil, sildenafil, tadalafil,udenafil, vardenafil, avanafil andtrazodone. The first line treatment of erectile dysfunction consists of a trial of PDE5 inhibitor drugs (the first of which was sildenafil or Viagra). They are available as tablet dosage forms commercially.How evertadalafil being poorly soluble may pose dissolution absorbtion problem resulting in poor bioavailabilty of the drug there for difficulty to currently erectiledysfunction. [3]

Tadalafil is used to treat erectile dysfunction in men and it is a selective inhibitor of cyclicguanosine monophosphate (cGMP)and specific phosphodiesterase type5(PDE 5) Chemically, tadalafil is pyrazino [1', 2': 1,6] pyrido [3,4-b] indole-1, 4-dione, 6-(1,3-benzodioxon–5-yl)–2,3,6,7,12,12a-hexahydro- methyl- (6R, 12aR). It is not official in any of the pharmacopoeia.Tadalafil is a PDE5 inhibitor, currently marketed in pill form for treating erectile dysfunction (ED) under the name Cialis; and under the name Adcirca for the treatment of pulmonary arterial hypertension. The approved dose for pulmonary arterial hypertension is 40 mg (two 20-mg tablets) once daily. Tadalafil is also manufactured and sold under the name of Tadacip by the Indian pharmaceutical company Cipla in doses of 10mg and 20 mg.Pharmacologic distinction is its longer half-life (17.50 hours) – compared to

Viagra (4.0–5.0 hours) and Levitra (4.0–5.0 hours) – resulting in longer duration of action, and so partly responsible for "The Weekend Pill" sobriquet.[4]

Furthermore, the longer half-life is the basis for current investigation of tadalafil's daily therapeutic use in relieving pulmonary arterial hypertension. Currently, sildenafil (trade name Revatio) is approved in several world regions as a thrice-daily therapy for pulmonary arterial hypertension. Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and the smooth muscle of the corpus cavernosum. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP relaxes smooth muscle and increases blood flow to the corpus caver nosum. The inhibition of phosphodiesterase type 5 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil,sildenafil and vardenafil inhibits PDE5.[5]

However, because sexual stimulation is required to initiate the local penile release of nitric oxide, tadalafil's inhibition of PDE5 will have no effect without direct sexual stimulation of the penis. The recommended tadalafil starting dose for most men is 10 mg, taken as needed before sexual activity (but not more than once daily).The dose may be increased to 20 mg or decreased to 5 mg, per its efficacy and the man's personal tolerance of the drug. To avoid the inconvenience of a man having to program and plan using tadalafil around the time of his anticipated sexual activity, In patients with pulmonary arterial hypertension, the pulmonary vascular lumen is decreased as a result of vasoconstriction and vascular remodeling, resulting in increased pulmonary artery pressure and pulmonary vascular resistance. Jellies are transparent, opaque, non-greasy semisolid gels generally applied externally. They are used for medication, lubrication and some miscellaneous application. Gelling agent used normally are tragacanth, sodium alginate, pectin, starch, gelatin, cellulose derivative like hydroxy propyl methyl cellulose (HPMC), methyl cellulose (MC), carbomer, polyvinyl pyrrolidone.[6]

2. REVIEW OF THE LITERATURE

Erectile dysfunction (ED, impotence) and premature ejaculation (PE) are the two main complaints in male sexual medicine. New oral therapies have completely changed the diagnostic and therapeutic approach to ED and the guidelines office of the European Association of Urology (EAU) has appointed an expert panel to update previously published EAU guidelines for ED or impotence. Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain and/or maintain penile erection sufficiently for a sexual activity. A 3-month minimum duration is accepted for the establishment of the diagnosis. Several studies have provided data on the prevalence of ED. The prevalence of ED on a worldwide basis has a great deal of variation around 9%-69%. And, there is a clear increase of this disorder at older ages. In all studies, ED has a rather high rate from 20% to 40% for the ages 60 to 69 years old, some increasing after the age of 65 years old. Erectile Dysfunction (ED) or male impotence is defined as the inability to develop or maintai n an erection sufficienfor satisfactory sexual performance.[7]

Epidemiology of Erectile dysfunction

Erectile dysfunction is a significant and common medical problem. Recent epidemiologic studies suggest that approximately 10% of men aged 40-70 have severe or complete erectile dysfunction, defined as the total inability to achieve or maintain erections sufficient for sexual performance. An additional 25% of men in this age category have moderate or intermittent erectile difficulties. The disorder is highly age-dependent, as the combined prevalence of moderate to complete erectile dysfunction rises from approximately 22% at age 40 to 49% by age 70. Although less common in younger men, erectile dysfunction still affects 5%-10% of men below the age of 40. Findings from these studies show that erectile dysfunction impacts significantly on mood state, interpersonal functioning, and overall quality of life.[8]

Erectile dysfunction is strongly related to both physical and psychological health. Among the major risk factors are diabetes mellitus, heart disease, and hypertension and decreased HDL levels. Medications for diabetes, hypertension, cardiovascular disease and depression may also cause erectile difficulties. In addition, there is a higher prevalence of erectile dysfunction among men who have undergone radiation or surgery for prostate cancer, or who have a lower spinal cord injury or other neurological diseases (e.g. Parkinson's disease, multiple sclerosis). Life style factors, including smoking, alcohol consumption and

sedentary behavior are additional risk factors. The psychological correlates of erectile dysfunction include anxiety, depression and anger. Despite its increasing prevalence among older men, erectile dysfunction is not considered a normal or inevitable part of the aging process. It is rarely (in fewer than 5% of cases) due to aging-related hypogonadism, although the relationship between erectile dysfunction and age-related declines in androgen remains controversial.[9]

Erectile impairment is a condition with profound psychological consequences and may interfere with a man's overall well-being, self-esteem and interpersonal relationships. Conservative estimates of its incidence have been made at between 10-20 million men. Furthermore, it has been shown that erectile problems account for 400,000 out-patient physician visits, 30,000 hospital admissions and an annual financial outlay by our health industry of 146 million dollars. Kinsey's report in 1948 was the first study to address the occurrence of sexual dysfunction in the general population. Results from this study, based on the detailed interview of 12,000 males, stratified for age, education and occupation, indicated an increasing rate of impotence with age. Its prevalence was cited as less than 1% in men under 19 years of age, 3% of men under 45 years, 7% less than 55 years and 25% by the age of 75 years. In 1979, Gerhard reanalyzed the Kinsey data and in a chart of over five thousand men, 42% admitted to erectile difficulties. As the number of vascular risk factors (such as, cigarette smoking, hypertension, cardiac disease, hyperlipidemia, and diabetes) increases so too does the likelihood of erectile dysfunction. This finding was confirmed in Virago's analysis of 400 impotent men, demonstrating that 80% of these men had physiologic abnormalities and that vascular risk factors were more common in this group compared to the general population.

While androgens are essential to the growth and differentiation of the male genital tract, the development of secondary sexual characteristics and the presence of libido their role in the erectile process remains unclear. At this time, the nature of an appropriate hormonal investigation, whether a complete hormone panel is required for every patient or whether a single testosterone determination constitute effective screening remains debated. Indeed, disagreement exists on whether free or total testosterone levels are more important in he evaluation of the impotent male. Nevertheless, endocrinopathies probably account for up between 3-6% of all organic erectile dysfunction and those endocrinopathies that may lead to

impotence include hypogonadism, hypothyroidism, hyperthyroidism, hyperprolactinemia, diabetes mellitus, adrenal disorders, chronic liver disease, chronic renal failure and AIDS.[10]

Drug associated erectile dysfunction is common and the list of medications that can induce erectile dysfunction is significant. Medication-induced impotence has been estimated occurring in up to 25% of patients in a medical outpatient clinic. Antihypertensive agents are associated with erectile difficulties, depending upon the specific agents in 4-40% of patients. They induce impotence either by actions at the central level (clonidine), by direct actions at the corporal level (calcium channel blockers) or by purely dropping systemic blood pressure upon which the patient has relied to maintain an intracorporal pressure sufficient for the development of penile rigidity.

Several medications cause impotence based on their anti-androgen actions, for example estrogens, LHRH agonists, H2 antagonists, and spironolactone. Digoxin induces erectile difficulties via blockade of the NA-K-ATP as pump resulting in a net increase in intracellular Ca and subsequent increased tone in the caporal smooth muscle. The psychotropic medications alter CNS mechanisms. Chronic use of recreational drugs has been associated with erectile dysfunction. Other agents affect erection through, as of yet, unknown mechanisms. Ultimately, it is essential to define a mechanism for each medication suspected of causing impotence. Furthermore, the diagnosis of drug-induced erectile dysfunction must be predicated upon reproducibility of the problem with medication administration and cessation of the problem upon its discontinuation. Apart from the factors already outlined (vascular risk factors, endocrinopthies and psychological problems) that may lead to impotence the following conditions may induce erectile problems. Renal Failure: Up to 40% of men suffering from chronic renal failure have some form of erectile dysfunction.[11]

The mechanism by which impotence results in this disorder is probably multifactorial, involvingendocrinologichypogonadism, hyperprolactinemia; neuropathicdiabetes induced nephropathy and vascular factors. Hatzichristou investigated the vascular etiologies in a cohort of men with chronic renal failure who had undergone hemodynamic evaluation and found an inordinately high incidence of corporovenoclusive dysfunction. The role of renal transplantation in the development of erectile dysfunction in these patients is variable. In some, transplant improves the renal function to the point where the patients' erectile function also improves and in others, particularly those men who had received 2 transplants, the erectile function may deteriorate further.

Neurologic disorders: Neurogenic erectile dysfunction may be caused by disorders such as, stroke, brain and spinal tumors, cerebral infection, Alzheimer's disease, temporal lobe epilepsy and multiple sclerosis (MS). Agarwal cited a 85% incidence of impotence in a group of men following stroke, while Goldstein noted 71% of men with MS were affected by erectile difficulties. More recently, it has beenn recognized that AIDS has associated with an autonomic neuropathy which may cause neurogenic erectile dysfunction.Pulmonary diseases: Fletcher noted a 30% incidence of impotence in men with chronic obstructive pulmonary disease (COPD), all of whom had normal peripheral and penile pulses by Doppler assessment,suggestingthe COPD was the primary etiologic factor.Systemic disorders: Apart from diseases already mentioned (diabetes, vascular diseases, renal failure) some other disorders are associated with impotence. Scleroderma may result in erectile dysfunction as a result of the small vessel vasculopathy that it causes. Chronic liver disease has been associated with erectile impairment in up to 50% of patients with this disorder. this incidence is somewhat dpendent on the etiology of the liver dysfunction, alcoholic liver disease having a higher incidence than non-alcoholic.[12]

Mechanism Of Erectile Dysfunction

The word Impotence is derived from the Latin language and literally means loss of power. The word is also used to show an inability to do anything about a certain situation. Erectile functions is a very complicated process and while getting an erection might appear to be simple for most men the mechanisms and functions going on are elaborate and complex. The actual structure of the penis for example consists of a number of different components. Firstly there are the corpus cavernous which are 2 columns made up of spongy tissue, then there is the corpus spongiosum that is a spongy chamber that contains the tube which allows urine to flow from the bladder into the penis.The erectile tissue that makes up these structures is full of tiny blood vessels known as cavernous sinuses and these blood vessels are covered by muscle and elastic fibrous tissue made up of collagen.The mechanism of an erection is also dependent on nitric oxide and when a man gets an erection his central nervous system allows the release of chemicals, the most important one being nitric oxide.

The nitric oxide boosts the the manufacture of cyclic GMP which is directly responsible for allowing the muscles in the penis to relax. With these muscles relaxed the blood can flow into the cavernous sinuses and this fills the penis with blood. When the penis is full of blood it will normally be double the it's previous size. The process also involves the

shutting down of the veins around the chambers locking the blood in them and keeping the erection hard and rigid. The nitric oxide is an essential part of the erection process and too much of it means that you are unable to get rid of your erection. After arousal and ejaculation the cyclic GMP has to be got rid of and an so an enzyme known as phosphodiesterase-5 (PDE5) forms which reacts with the cyclic GMP and removes it. In fact the main erectile dysfunction drugs Viagra, Cialis and Levitra are known as PDE-5 inhibitors as they shop the formation of the PDE-5 which means that the erection will be sustained.[13]

Other factors are also essential for the efficient working of an erection. The right balance of the hormone testosterone and oxygen rich blood as well as healthy and unblocked arteries are also needed for good erectile function. Psychological factors can also play a part on making sure that your erection functions properly. Most men have no idea of the complicated issues involved sustaining an erection and are unaware that they need to maintain good sexual health in order to keep functioning well sexually.

Statistics on Male Sexual Dysfunction

Erectile dysfunction is estimated to effect 150 million men worldwide, and more than one million men in Australia. Overall, 25% of Australian men report erectile dysfunction and 8.5% report severe erectile dysfunction. In one study, 9.6% reported 'occasional' erectile dysfunction, 8.9% reported erectile dysfunction occurring 'often', and 18.6% reported erectile dysfunction occurring 'all the time'. Of these, only 11.6% had received treatment. In another study, only 14.1% of men reported that they had received treatment, despite experiencing erectile dysfunction for longer than 12 months.

Erectile dysfunction is never 'normal', however it does become more common and more severe as men age. One Australian study reported the rate of erectile dysfunction in different age groups:

AGE	PERCENTAGE
20-29	9.2
30-39	8.4
40-49	13.1
50-59	33.5
60-69	51.5
70-79	69.2
80_{+}	76.2

Due to the ageing Australian population, erectile dysfunction is expected to become more common. There is no difference between the prevalence of erectile dysfunction between "white-collar" and "blue-collar" workers in Australia.[14]

Sexual dysfunction associated with cancer

Between 10 and 88% of patients diagnosed with cancer experience sexual problems following diagnosis and treatment. The prevalence varies according to the location and type of cancer, and the treatment modalities used. Sexuality may be affected by chemotherapy, alterations in body image due to weight change, hair loss or surgical disfigurement, hormonal changes, and cancer treatments that directly affect the pelvic region. Sexual problems are reported in many patients with prostate and testicular cancer. They are also reported in patients with cancer that does not directly affect sexual organs, including lung cancer (48% of patients),Hodgkin's disease (50%),laryngeal (%60) and head and neck cancers (39-74%).Below are some statistics that you may find helpful to be able to learn more about your condition.

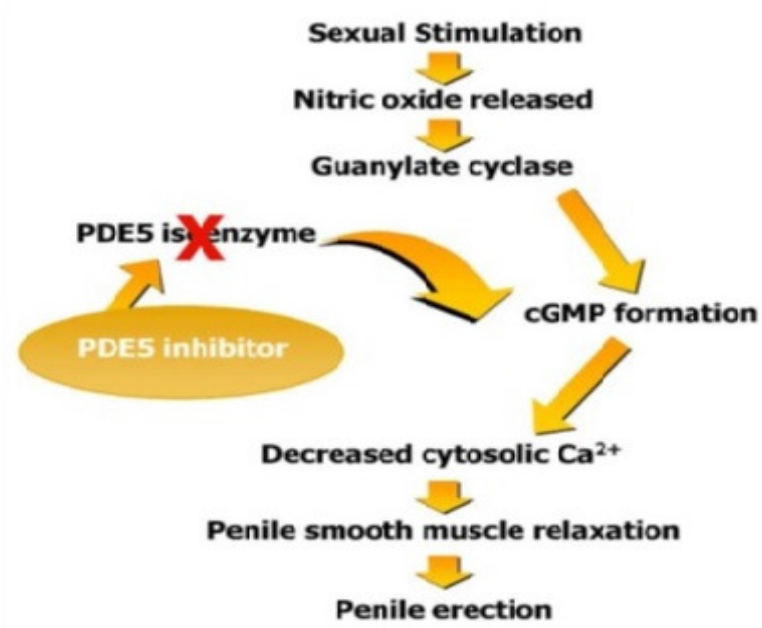
Statistics

- 1 in 10 men in the world are thought to suffer from erectile dysfunction.
- It is estimated that half of all men who have diabetes suffer from erectile dysfunction.
- If a man smokes more than 1 packet of cigarettes per day then they have a 50% higher chance of erectile problems than a man who is a non-smoker.
- Men over the age of 75 have a 77.5% chance of suffering from erectile problems.
- Men between the ages of 20 and 29 only have a 6.5% chance of having erectile problems.

- It is thought that erectile dysfunctions cause the breakdown of 20% of all relationships.
- A shocking estimate is that only 33% of men who have erectile dysfunctions seek help and advice about their problems.
- If you have problems with your erections 20% or less of the time then it is unlikely that you will need treatment.
- Over 20 million men all over the world have used or are currently using Viagra to treat erectile dysfunction.
- In 66% of the times that Viagra is taken, men are able to have sexual intercourse.
- 48% of men suffer one or more side effects when using Viagra.
- Underlying health issues such as diabetes or heart disease account for 70% of all erectile dysfunction cases.
- Psychological causes such as stress and anxiety are estimated to cause around 10 % to 20% of all erectile dysfunction cases.
- It is estimated that in 80% of all cases the causes of erectile problems are down to physical reasons.[15]

ROLE OF TADALAFIL IN ERECTILEDYSFUNCTION:-

Tadalafil is currently approved in at least 90 countries as an oral treatment for erectile dysfunction (ED). It is marketed throughout the world as Cialis1 (pronounced ‘‘See-AL-is’’).In Saudi Arabia, tadalafil is marketed as bothCialis1 and Snafi1.Tadalafil is an inhibitor of PDE5. After entering smooth muscle cells in arteries within the corpus cavernosum of the penis, tadalafil competitively inhibits PDE5, and prevents the inactivation of the intracellular messenger cGMP. Consequently, by inhibiting PDE5 in the corpus cavernosum, tadalafil prolongs the action of cGMP, facilitating the erectile response to sexual stimulation. Supplement.[16]



APPROACHES TO IMPROVE THE TADALAFIL (RELATED WORKS)

Vikrant Vyas et al., [17] (2009) Dissolution behaviour of a poorly water-soluble drug, tadalafil, from its solid dispersion systems with poloxamer 407 has been investigated. Solid dispersion systems of tadalafil were prepared with poloxamer 407 in 1:0.5, 1:1.5 and 1:2.5 ratios using the melting method. Characterization of binary systems with FTIR and XRPD studies demonstrated the presence of strong hydrogen bonding interactions, a significant decrease in crystalline and the possibility of existence of amorphous entities of the drug. In the binary systems tested, 1:0.5 proportion of tadalafil/poloxamer 407 showed rapid dissolution of tadalafil (DE30 70.9 ± 3.6 %). In contrast, higher proportions of poloxamer 407 (1:1.5 and 1:2.5) offered no advantage towards dissolution enhancement of the drug, indicating altered rheological characteristics of the polymer at its higher concentration, which might have retarded the release rate of tadalafil.

N. Kannappan et al [18] (2010) in the present study simple, reliable and reproducible HPLC methods were developed for the analysis of Tadalafil and Sildednafil citrate (API). The column used was YMC-Pack ODS AQ (150 mm x 4.6 mm,i.d.).The mobile phase used was phosphate buffer (10mM, pH 3.0) acetonitrile gradient run at the flow rate of 1mL/min

with UV (PDA) detector at 220nm at ambient temperature. Extraction of Tadalafil and Sildenafil citrate from tablet was carried out using methanol. Linearity was observed in the range from 50 to 150µg/ml for tadalafil with a correlation coefficient (R2) 0.99 and 10ng/ml as the limit of detection. The values of linearity range, correlation coefficient (R2) and limit of detection were 50 to 150µg/ml, 0.99 and 20ng/ml respectively for sildenafil. Parameters of validation prove the precision and stability of the method and it's applicability for the Assay of tadalafil and sildenafil citrate. The method is suitable for routine analysis of the drug**.**

V. Ravi Kumar et al [19] (2012) in the present study to enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Tadalafil a BCS class II drug is an impotence agent. It is indicated for the treatment of erectile dysfunction and is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type-5 (PDE-5).However, insolubility and poor dissolution of this molecule, delays its rate of absorption and finally the onset of action. Solid dispersion has been successfully utilized as dissolution enhancement technique using water soluble polymers for wide variety of poorly water-soluble drugs. The present study aims at enhancement of dissolution profile of Tadalafil using PVP K30 and PEG 6000 as carriers by solid dispersion technique. Solid dispersion containing Tadalafil was further investigated by drug content*, in-vitro* drug release, FTIR, DSC, XPRD and SEM analysis. Absence of significant drug-carrier interaction was confirmed by IR and DSC data. XPRD reveals that crystallinity nature of Tadalafil was decreased. From the study it was concluded that the *in-vitro* dissolution of Tadalafil can be enhanced by solid dispersion technique.

T. VaniPrasanna et al [20] (2012) in the present studyTadalafil (TD), a PDE-5 inhibitor, belongs to BCS class II. It is poorly soluble in water and requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. In the present investigation, solid dispersed systems of tadalafil with poloxamer188 and sodium starch glycolate were prepared using solvent evaporation technique. The dissolution rate of the drug and poloxamer188 based solid dispersion was significantly higher than the sodium starch glycolate (SSG) based preparations and pure drug which reaches closer to the dissolution profile of marketed product. This was due to an increase in surface area of drug available for dissolution. Characterization of binary systems with FTIR studies demonstrated the presence of strong hydrogen bonding interactions, a significant decrease in crystallinity and the possibility of existence of amorphous entities of the drug. In the binary systems tested, 1:0.5

proportion of Tadalafil/poloxamer188 showed rapid dissolution of tadalafil (*DE*30 56.68 %). In the binary systems, tested (1:0.5) proportion of tadalafil/poloxamer188 showed rapid dissolution of tadalafil. In contrast, higher proportion of polaxmer188 (1:1) offered no advantage towards dissolution enhancement of the drug, indicating altered rheological characters of the polymer at its higher concentration, which might have retard the release rate of tadalafil. The tablets were prepared for the optimized formula of solid dispersion, by wet granulation technique. The solid dispersion tablets were evaluated and compared with tadalafil marketed product.

K.MallikarjunaRao et al [21] (2012) in the present study Fast dissolving tablets are solid tablets and designed to dissolve/disintegrate in the patient's mouth within few seconds or minutes, without the need to drink or chew Tadalafil. The Main aim of the present study was prepare fast dissolving tablets of Tadalafil in the oral cavity with enhanced dissolution rate. The fast dissolving tablets of zidovudine was prepared with different concentrations of ingredients such as SSG and crosspovidone as superdisintegrants and ß-Cyclodextrin as a solubilizing agent by using direct compression technique. The prepared tablets were evaluated for the different evaluation parameters such as angle of repose, compressible index, hausner's ratio, percentage of drug content, hardness, thickness, friability, *In-Vitro* disintegration, *In-Vitro* dissolution and stability studies. The evaluation parameters of the prepared formulations results were obtained the satisfactory results. From the all the formulations, formulation (ODTT-VIII) was found to be the best formulations, based upon the In-Vitro drug release studies

Gudipati Edukondalu et al [22] (2012) in the present study simple, precise and accurate RP-HPLC method was developed and validated for rapid assay of Tadalafil tablet dosage form. Isocratic elution at a flow rate of 1.3ml/min was employed on a symmetryChromosil C18 (250x4.6mm, 5µm in particle size) at ambient temperature. The mobile phase consisted of Methanol: Acetonitrile 65:35 v/v. The UV detection wavelength was 222 nm and 20µl sample was injected. The retention time for Tadalafil was 7.8 min. The percentage RSD for precision and accuracy of the method was found to be less than 2%. The method was validated as per the ICH guidelines. The method was successfully applied for routine analysis of Tadalafil tablet dosage form and bulk drug.

Sabry kh. Mohamed*et al [23] (2013) in the present study Ion – associate complexes of sildenafil, tadalafil and vardenafil hydrochlorides with [Manganese (II) and Cobalt (II)] thiocyanates, potassium ferricyanide, sodium cobaltinitrite and ammonium reineckate were precipitated and the excess unreacted metal complex was determined. A new method using atomic emission and atomic absorption spectrometry for the determination of the above drugs in pure solutions, in pharmaceutical preparations and urine of diabetic patient's type 2 was given. The drugs can be determined by the affort method in the ranges 0.56 - 104.28, 0.64 - 117.81 and 0.63 – 115.39 µg mL-1 solutions of Sd, Td and Vd, respectively.

Vinesha et al [24] (2013) co-crystallization is an emerging method to optimize physicochemical properties of pharmaceutically active compounds including dissolution rate and stability. The main aim of this study was to increase the solubility by co crystal approach and characteristic the co-crystal (1:1) involving tadalafil and salicylic acid which were prepared by solvent evaporation method. The prepared co-crystals showed increase solubility than pure drug.

Wasfy M. Obeidat et al [25] (2013) The aim of this work was to prepare and evaluate Tadalafilnanosuspensions and their PEG 4000 solid dispersion matrices to enhance its dissolution rate. Nanosuspensions were prepared by precipitation/ultrasonication technique at 5°C where different stabilizers were screened for stabilization. Nanosuspensions were characterized in terms of particle size and charge. Screening process limited suitable stabilizers into structurally related surfactants composed of a mixture of Tween80 and Span80 at 1:1 ratio (in percent, weight/volume) in adjusted alkaline pH (named TDTSp-OH). The surfactant mixture aided the production of nanosuspensions with an average particle size of 193 ± 8 nm and with short-term stability sufficient for further processing. Solid dispersion matrices made of dried Tadalafil nanosuspensions or dried Tadalafil raw powder suspensions and PEG 4000 as a carrier were prepared by direct compression. Drying was performed via dry heat or via freeze dry. Drug release studies showed that, in general, tablet formulations made of freeze-dried product exhibited faster initial release rates than the corresponding tablets made of oven-dried products which could be attributed to possible larger crystal growth and larger crushing strengths of oven-dried formulations. At best, 60% of drug was released from solid dispersion matrices, while more than 90% of drug was released from TDTSp-OH nanosuspension within the first 5 min. In conclusion, tadalafil nanosuspensions

obtained using a mixed surfactant system provided rapid dissolution rates of Tadalafil that can theoretically enhance its bioavailability.

M.shanker et al [26] (2013) in the present study simple, selective, precise and stability indicating RP-HPLC method for the determination of tadalafil was developed and validated in oral jelly dosage forms. The chromatographic parameters comprised of Zorbax C18 column (250X4.6 mm, 5µ) and mixture of buffer: acetonitrile (55: 45 v/v) as mobile phase. The detection was observed at 225nm with 1.5 ml/min flow rate. The developed method has been validated according to ICH and USP guidelines. The linearity studies showed a good correlation over the range of 10 to 75 µg/ml with correlation coefficient (r2) of 0.998. The drug was subjected to forced degradation analysis on varied conditions of acidic, basic, peroxide, thermal, light and UV radiation. All the results have proved that the method was selective and reproducible for the determination of tadalafil. The proposed stability indicating RP-HPLC method can be effectively employed for the determination of tadalafil in routine drug analysis of oral jelly dosage forms

REALETED WORKS ON ORAL JELLY:-

D.K Jain* et al [27] (2008) In the present study Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Metformin hydrochloride and Glimepiride is orally administered antihyperglycemic agent, used in the management of non-insulin-dependent (type-2) diabetes mellitus. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly and pediatrics. Unfortunately, a high percentage of patients suffering from type-2 diabetes are elderly people showing dysphagia. Persons suffering from dysphagia may get choked when they consume liquid formulation, thus to alleviate such problem liquid formulation of high viscosity was prepared. Formulation of oral soft jellies was carried out using combination of hydrophilic polymers guar gum and pectin. 3 different concentrations of guar gum (0.3 to 0.5% w/v) and 2 concentration of pectin were used (0.2 to 0.3% w/v) respectively. The prepared batches were evaluated for appearance, viscosity, pH, drug content, syneresis, in vitro drug release, and taste masking. The batch with 0.5% w/v guar gum and 0.2% pectin not only showed 80% drug release at 60 min, but all the desired organoleptic properties. The taste masking was carried out using non nutritive sugar and flavors. The optimized batch showed substantial stability when subjected to short term stability study (0-8°C and Room

temperature). The problem of dose measurement by patients was outweighed as oral medicated gels are to be packed in unit dose container.

Deborah Evangeline.D et al [28] (2011) In the present study medicated jelly with Ajowan extract was formulated using polymers like sodium alginate and tragacanth. The jellies were evaluated for their physiochemical parameters like pH, spreadability and stability studies. The antimicrobial activities of the gels were also carried out. Formulations using sodium alginate shows desired properties and significant antimicrobial activity. Ajowan is the dried ripe seed of Trachysperumammi (L), Sprague, belonging to the family Apiaceous .It has an agreeable taste and an aromatic odour. It is valued for its antiseptic, antispasmodic, stimulant, tonic and carminative properties. It is also effective in treating sore throat, bronchitis, diarrhoea and Cholera .Therefore, the present study was carried out to formulate a medicated jelly with ajowan extract by using different gelling agents like sodium alginate and tragcanth in various proportions. The jellies thus prepared were evaluated for their appearance, pH, spreadability, antimicrobial activity and also for its stability studies.

Thejomoorthy et al [29] (2012) In the present study analytical method based on Liquid-liquid extraction has been developed and validated for analysis of Tadalafilin rat plasma. Tadalafil-D3 was used as an internal standard. Zorbax-SB C18, 75 x 4.6 mm, 3.5 µm column provided chromatographic separation of analyte followed by detection with mass spectrometry. The method involves simple isocratic chromatographic condition and mass spectrometric detection in the positive ionization mode using an API-4200 system. The total run time was 3.0 minutes. The proposed method has been validated with linear range of 0.50–1000.00 ng/mL for Tadalafil. The intra-run and inter-run precision values are within 1.37 - 2.25% and 2.23- 5.31%. The overall recovery for Tadalafil and Tadalafil-D3 was 91.07% and 86.66%. This validated method was applied successfully in rat plasma samples for pharmacokinetic study**.**

Tanu Godhwani1 et al [30] (2012) In the present study was conducted with an aim to formulate and evaluate the unit molded jelly containing calcium supplement and optimization of this dosage form which will dissolve slowly when kept in contact with mouth without any irritation or inflammation and bitter after taste. The oral route of administration is the preferred route of drug delivery. Now-a-days, jelly candies have become very common in children as they enjoy chewing the jelly. The formulation of jelly is advantageous for drug delivery in pediatric patients and may also be used in the cases where tablet or capsule swallowing is difficult. The jellies were evaluated for their physiochemical parameters like

Color, taste loss on drying, pH, spreadability, test for presence of heavy metals and stability studies. All the ten formulation (F1 to F10) under study was found to be stable and showed comparable appearance, pH, spreadability and viscosity. The article describes about the formulation aspect of jelly, excipients and flavors employed and the evaluation parameters along with the drug used in the formulation. The optimized formulation F4 was found to be stable for the period of 3 months as per ICH guidelines**.**

C.D.Nieuwoudt et al [31] (2012) Pharmacokinetics and Stability of an Enrofloxacin Oral Gel Formulation in Horses. Enrofloxacin, in an oral flavored gel formation, achieves clinically effective serum concentrations necessary to treat susceptible infections in horses. The formulated gel retains full potency for a 3-mo period. Oral antibiotic choices to treat infections in horses are limited. In many cases, such as peritonitis, osteomyelitis, or pleura pneumonia, to name a few, long-term therapy may be necessary. In instances where owners need to administer the antibiotic doses, the IV or IM route may be difficult or dangerous, and the oral route is preferable. Enrofloxacin is not only another alternative to the few antibiotics currently available to give orally to treat infections in horses, but also offers a broad spectrum of activity. The commercial enrofloxacin tablets, approved for use in dogs, are cumbersome to crush, and the volume of the cattle injection is large, resulting in loss of some of the dose when administered. We developed an oral flavoured gel formulation from the cattle injection that significantly eased administration of the dose. The purpose of this study was to determine whether enrofloxacin achieves clinically sufficient serum concentrations after oral administration of the gel formulation. In addition, the stability of the extemporaneous formulation was studied.

T. Salunke et al [32] (2013)In the Present study was aimed to formulate and evaluate medicated Jelly of Bitter drugs i.e. Ofloxacin and Ornidazole. For taste masking of Ofloxacin, ion-exchange resin method was used. The resins like Indion 204, Indion 214 and Tulsion 335 was tested at various ratios. Based on the results Tulsion 335 with the ratio 1:1.5 was selected for complexation. For taste masking of Ornidazole, addition of sweetening agent method was used. The slurry was prepared using Sorbitol 70%, Polyethylene glycol 400 and Glycerin in the concentration of 10%, 6% and 7% respectively. It was observed that the batch F7 containing 0.4% Xanthan gum, 0.5% Carrageenan and 0.3% sodium citrate and shows satisfactory results. The optimized formulation F7 evaluated which shows satisfactory results. pH of the maximum stability of Ofloxacin and Ornidazole in aqueous phase is in between 5

to 6. The drug content of jelly of batches F1 to F9 was evaluated by HPLC method. The results are between 97.00% to 103.00% for Ofloxacin and 95.00 % to 104.00 for Ornidazole. The dissolution studies of the Medicated jelly for all the formulations show more than 70% drug release at 20 minutes time point and complete drug release within 45 minutes. The optimized formulation F7 kept for the three month at storage condition and it was evaluated with similar test as per initial analysis which shows satisfactory results.

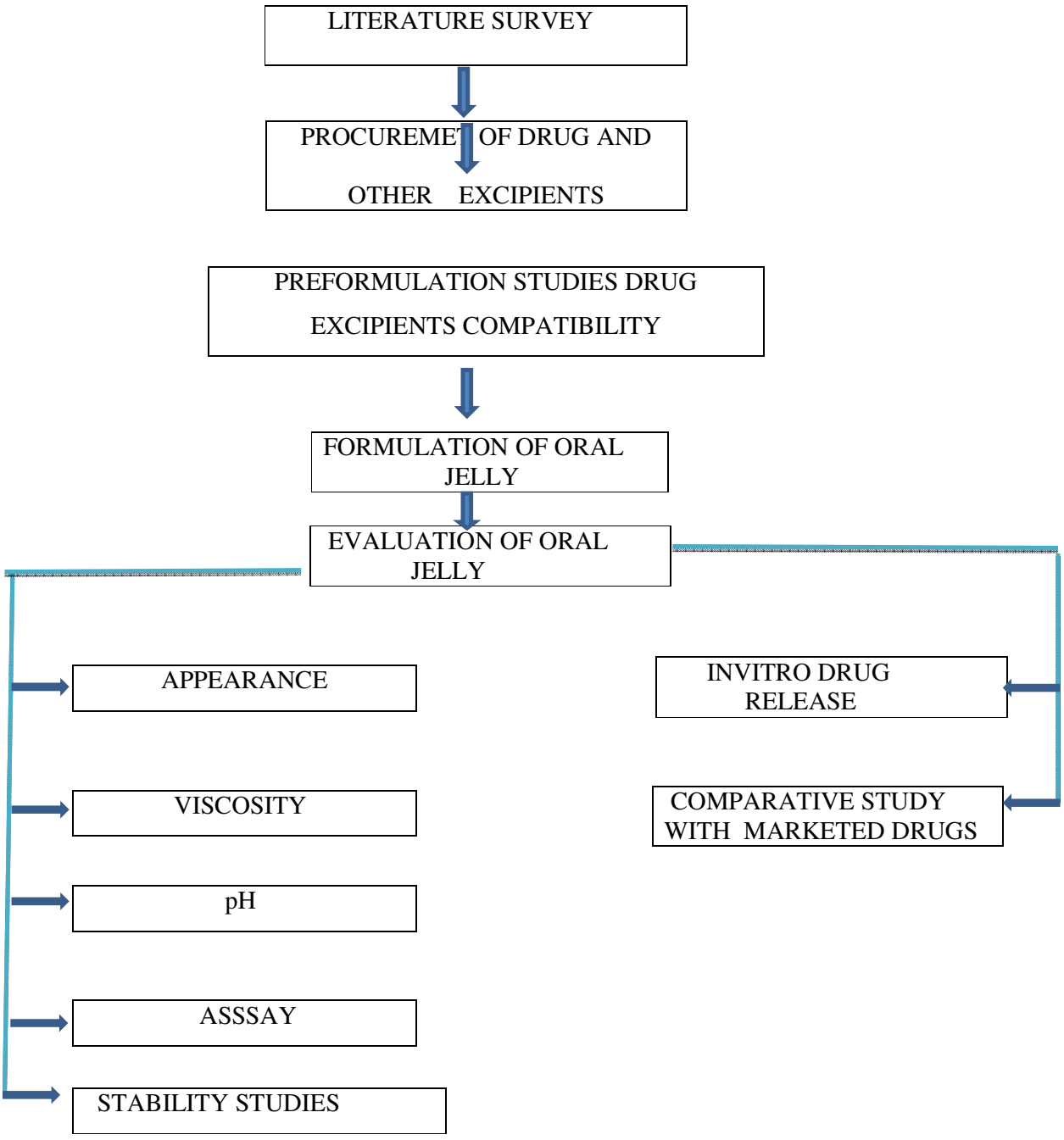
4. AIM AND OBJECTIVE OF THE STUDY

The present aimed to formulate and evaluate comparison tadalafil oral jellies for erectile dysfunction with marketed product.

OBJECTIVES OF THE STUDY:

- Preparation of standard curve
- Formulation of tadalafil oral medicated jelly by using simple mixing.
- Characterization of the prepared medicated jellies for its odour, taste, pH, viscosity, drug content and invitro drug release.
- Stability studies for best formulations.
- Release Kinetics.

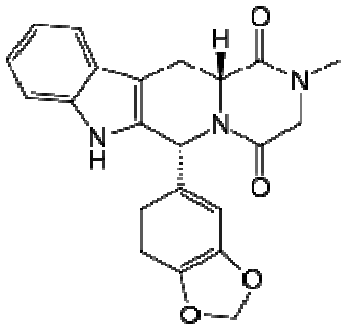
5. PLAN OF WORK



6.1 DRUG PROFILE

Tadalafil

Class	**:**	Phosphodiesterase type 5 inhibitor [33]
IUPAC Name	**:**	(6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro- 2-methyl-pyrazino [1', 2':1,6] pyrido[3,4- b]indole-1,4-dione
Molecular formula	**:**	$C_{22}H_{19}N_3O_4$
Molecular weight	**:**	389.404 g/mol
Structure	**:**	



Melting point	**:**	301-302^0 C
Half-life	**:**	17.5hrs
Protein binding	**:**	94%
Solubility	**:**	Practically insoluble in water & very slightly soluble in ethanol
Route	**:**	Oral
Adverse reactions	**:**	Dyspepsia, Back pain, Myalgia, Nasalcongestion, Flushing, Pain in limb
Excretion	**:**	Urine > 30%,Feces> 60%

Mechanism of Action

Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates 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 (PDE5) enhances erectile function by increasing the amount of cGMP. Tadalafil inhibits PDE5. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 by tadalafil has no effect in the absence of sexual stimulation. Studies in vitro have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas. In vitro studies have shown that the effect of tadalafil is more potent on PDE5 than on other phosphodiesterases.

Pharmacodynamics

Tadalafil is used to treat male erectile dysfunction (impotence) and pulmonary arterial hypertension (PAH). Part of the physiological process of erection involves the release of nitric oxide(NO) in the corpus cavernosum. This then activities the enzyme quanylatecyclase which result in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation in the corpus cavernosum, resulting in increased inflow of blood and an erection. Tadalafil is a potent and selective inhibitor of cGMP specific phosphodiestrase type 5(PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. This means that with tadalafil on board, normal sexual stimulation leads to increased level of cGMP in the corpus cavernosum which leads to better erections. Without sexual stimulation and no activation of the NO/cGMP system the tadalafil should not causes an erection.

Pharmacokinetics

Over a dose range of 2.5 to 20 mg, tadalafil exposure (AUC) increases proportionally with dose in healthy subjects. Steady-state plasma concentrations are attained within 5 days of once-daily dosing, and exposure is approximately 1.6-fold greater than after a single dose. Tadalafil is eliminated predominantly by hepatic metabolism, mainly by cytochrome P450

3A4 (CYP3A4). The concomitant use of potent CYP3A4 inhibitors such as ritonavir or ketoconazole resulted in significant increases in tadalafil AUC values.

Absorption

After single oral-dose administration, the maximum observed plasma concentration (Cmax) of tadalafil is achieved between 30 minutes and 6 hours (median time of 2 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined. The rate and extent of absorption of tadalafil are not influenced by food; thus CIALIS may be taken with or without food.

Distribution

The mean apparent volume of distribution following oral administration is approximately 63 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins. Less than 0.0005% of the administered dose appeared in the semen of healthy subjects.

Metabolism

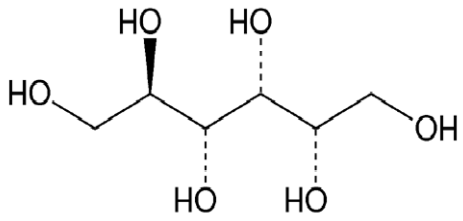
Tadalafil is predominantly metabolized by CYP3A4 to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatecholglucuronide conjugate, respectively. The major circulating metabolite is the methylcatecholglucuronide. Methylcatechol concentrations are less than 10% of glucuronide concentrations. In vitro data suggests that metabolites are not expected to be pharmacologically active at observed metabolite concentrations.

Elimination

The mean oral clearance for tadalafil is 2.5 L/hr and the mean terminal half-life is 17.5 hours in healthy subjects. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose)

6.2 EXCIPIENTS PROFILE

SORBITOL

Nonproprietary Names BP	**:**	Sorbitol JP: D-Sorbitol PhEur: Sorbitol USP-NF: Sorbitol
Synonym	**:**	C*PharmSorbidex; E420; 1, 2, 3,4,5,6 hexanehexol; Liponic 70- NC; Liponic 76-NC; Meritol; Neosorb;
Chemical Name and CAS Registry Number	**:**	D-Glucitol [50-70-4]
Empirical Formula	**:**	$C_6H_{14}O_6$
Molecular Weight	**:**	182.17.
Structural Formula	**:**	
Functional Category	**:**	Humectant; plasticizer; stabilizing agent; Sweetening agent; tablet and capsule diluent.

Applications in pharmaceutical formulation or technology

Sorbitol is widely used as an excipient in pharmaceutical formulations. It is also used extensively in cosmetics and food products. Sorbitol is used as a diluent in tablet formulations prepared by either wet granulation or direct compression. Sorbitol has been used as a plasticizer in film formulations. sorbitol is used as a vehicle in sugar-free formulations and as a stabilizer for drug.It has also been shown to be a suitable carrier to enhance the in vitro dissolution rate of indometacin. In syrups it is effective in preventing crystallization around the cap of bottles. Sorbitol is additionally used in injectable and topical preparations, and therapeutically as an osmotic laxative. Sorbitol may also be used analytically as a marker for assessing liver blood flow.

Description

Sorbitol is D-glucitol. It is a hexahydric alcohol related to mannose and is isomeric with mannitol. Sorbitol occurs as an odorless, white or almost colorless, crystalline, hygroscopic powder. Four crystalline polymorphs and one amorphous form of sorbitol have been identified that have slightlydifferentphysicalproperties,e.g.meltingpoint.Sorbitolis available in a wide range of grades and polymorphic forms, such as granules, flakes, or pellets that tend to cake less than the powdered form and have more desirable compression characteristics. Sorbitol has a pleasant, cooling, sweet taste andhasapproximately50–60% of the sweetness of sucrose.

Stability and storage conditions

Sorbitol is chemically relatively inert and is compatible with most excipients. It is stable in air in the absence of catalysts and in cold, dilute acids and alkalis. Sorbitol does not darken or decompose at elevated temperatures or in the presence of amines. It is non-flammable, noncorrosive, and non-volatile. Although sorbitol is resistant to fermentation by many micro- organisms, a preservative should be added to sorbitol solutions. Solutions may be stored in glass, plastic, aluminium, and stainless steel containers. Solutions for injection may be sterilized by autoclaving. The bulk material is hygroscopic and should be stored in an airtight container in a cool, dry place.

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Incompatibilities

Sorbitol will form water-soluble chelates with many divalent and trivalent metal ions in strongly acidic and alkaline conditions. Addition of liquid polyethylene glycols to sorbitol solution, with vigorous agitation, produces a waxy, water-soluble gel with a melting point of 35–408C. Sorbitol solutions also react with iron oxide to become discolored. Sorbitol increases the degradation rate of penicillin's in neutral and aqueous solutions.

Method of manufacture

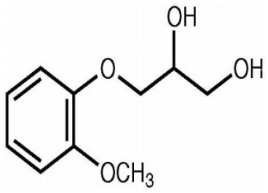
Sorbitol occurs naturally in the ripe berries of many trees and plants.It was first isolated in1872fromtheberries of theMountain Ash (Sorbusamericana). Industrially, sorbitol is prepared by high-pressure hydrogenation with a copper–chromium or nickel catalyst, or by electrolytic reduction of glucose and corn syrup. If cane or beet sugars are used as a source, the disaccharide is hydrolyzed to dextrose and fructose prior to hydrogenation.

Safety

Sorbitol is widely used in a number of pharmaceutical products and occurs naturally in many edible fruits and berries. It is absorbed more slowly from the gastrointestinal tract than sucrose and is metabolized in the liver to fructose and glucose. Its caloric value is approximately 16.7J/g (4cal/g).

PROPYLENE GLYCOL

Nonproprietary Names BP	**:**	Propylene Glycol JP: Propylene Glycol PhEur: Propylene Glycol USP: Propylene Glycol
Synonyms	**:**	1,2Dihydroxypropane; E1520; 2hydroxy propanol; methyl ethyl- ene glycol; methyl glycol; propane-1,2-diol; propylenglycolum.
Chemical Name and	**:**	1, 2-Propanediol [57-55-6] ()-1, 2-Propanediol
CAS Registry Number		[4254-14-2] (þ)-1, 2-Propanediol [4254-15-3] 4
Empirical Formula	**:**	$C_3H_8O_2$
Molecular Weight	:	76.09
Structural Formula	**:**	



Functional category

Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizing agent; water-miscible cosolvent.

Applications in pharmaceutical formulation or technology

Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. It is a better general solvent than glycerin and dissolves a wide variety of materials, such as corticosteroids, phenols, sulfa drugs, barbiturates, vitamins (A and D), most alkaloids, and many local anesthetics. As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations. Propylene glycol is also used in cosmetics

and in the food industry as a carrier for emulsifiers and as a vehicle for flavours in preference to ethanol, since its lack of volatility provides a more uniform flavour.

Description

Propylene glycol is a clear, colourless, viscous, practically odourless liquid, with a sweet, slightly acrid taste resembling that of glycerine.

Stability and storage conditions

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tendstooxidize,givingrise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid. Propylene glycol is chemically stable when mixed with ethanol (95%), glycerine, or water; aqueous solutions may be sterilized by autoclaving.

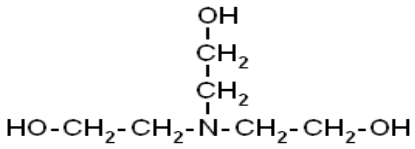
Propylene glycol is hygroscopic and should be stored in a well- closed container, protected from light, in a cool, dry place.

Incompatibilities

Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate.

TRIETHANOLAMINE

Nonproprietary Names BP	**:**	TriethanolaminePhEur:Trolamine USP-NF: Trolamine
Synonyms	**:**	TEA;Tealan; trihydroxytriethylamine; tris (hydroxyethyl)amine; trolaminum.
Chemical Names and	**:**	2, 20,200-Nitrilotriethanol [102-71-6]
Empirical Formula	**:**	$C_6H_{15}NO_3$
Molecular Weight	**:**	149.19
Structural Formula	**:**	



triethanolamine (TEA)

Functional category	**:**	Alkalizing agent, emulsifying agent.

Applications in pharmaceutical formulation or technology

Tri ethanolamine is widely used in topical pharmaceutical formulations, primarily in the formation of emulsions. When mixed in equimolar proportions with a fatty acid, such as stearic acid or oleic acid, triethanolamine forms an anionic soap with a pH of about8, which may be used as an emulsifying agent to produce fine-grained, stable oil-in-water emulsions. Concentrations that are typically used for emulsification are 2–4% v/v of tri ethanolamine and 2–5 times that of fatty acids. In the case of mineral oils, 5% v/v of triethanolamine will be needed, with an appropriate increase in the amount of fatty acid used. Preparations that contain triethanolamine soaps tend to darken on storage. However, discoloration may be reduced by avoiding exposure to light and contact with metals and metal ions. Triethanolamine is also used in salt formation for injectable solutions and in topical analgesic

preparations. It is also used in sun screen preparations.(1) Triethanolamine is used as an intermediate in the manufacturing of surfactants, textile specialties, waxes, polishes, herbicides, petroleum demulsifies, toilet goods, cement additives, and cutting oils. Triethanolamine is also claimed to be used for the production of lubricants for the rubber gloves and textile industries. Other general uses are as buffers, solvents, and polymer plasticizers, and as a humectants.

Description

Triethanolamine is a clear, colourless to pale yellow-colour viscous liquid having slight ammonia Caldor. It is a mixture of bases, mainly 2, 20,200-nitrilotriethanol, although it also contains 2, 20- iminobisethanol (diethanolamine) and smaller amounts of 2-aminoethanol (monoethanolamine).

Stability and storage conditions

Triethanolamine may turn brown on exposure to air and light. The 85% grade of triethanolamine tends to stratify below 158C; homogeneity can be restored by warming and mixing before use. Triethanolamine should be stored in an airtight container protected from light, in a cool, dry place. See Mono ethanolamine for further information.

Incompatibilities

Triethanolamine is tertiary amine that contains hydroxyl groups. it is capable of undergoing reactions typical of tertiary amines and alcohols. Triethanolamine will react with mineral acids to form crystalline salts and esters. With the higher fatty acids, triethanolamine forms salts that are soluble in water and have characteristics of soaps. Triethanolamine will also react with copper to form complex salts. Discoloration and precipitation can take place in the presence of heavy metal chloride to replace the hydroxyl groups with halogens. The products of these reactions are very toxic, resembling other nitrogen mustards' salts.

SUCRALOSE:-

Non proprietary Names : Sucralose

Synonyms : Splenda; sucralosa; sucralosum;

Chemical Name : 1, 6 - Dichloro-1, 6 - dideoxy –

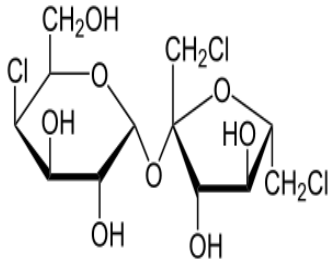
b- D - fructofuranosy l - 4- chloro

4 – deoxya – D - galactopyranoside

Empirical Formula : $C_{12}H_{19}C_{l3}O_8$

Molecular Weight : 397.64

Structural formula :



Functional Category : Sweetening agent.

Description : Sucralose is a white to

Off-white colored, free-flowing,

Crystalline powder.

Stability and storage conditions

Sucralose is a relatively stable material. In aqueous solution, athighly acidic conditions (pH < 3), and at high temperatures (4358C), it is hydrolyzed to a limited extent, producing 4-chloro-4-deoxygalactose and 1,6-dichloro-1,6-di deoxyfructose. In food products, sucralose remains stable throughout extended storage periods, even at low pH. However, it is most stable at pH 5–6. Sucralose should be stored in a well-closed container in a cool, dry place, at a temperature not exceeding 218C. Sucralose, when heated at elevated

temperatures, may break down with the release of carbon dioxide, carbon monoxide, and minor amounts of hydrogen chloride.

Applications in pharmaceutical formulation or technology

Sucralose is used as a sweetening agent in beverages, foods, and pharmaceutical applications. It has a sweetening power approximately 300–1000 times that of sucrose and has no aftertaste. It has nonutritional value, is noncariogenic, does not promote dental caries, and produces no glycemic response.

6.3. POLYMER PROFILE

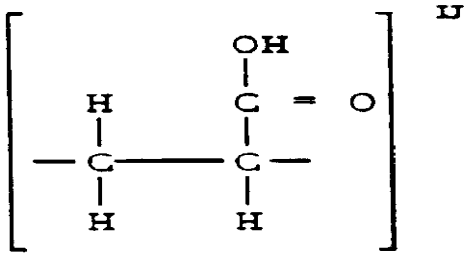
CARBOPOL 940

Synonym : Acritamer, Acrylic acid polymer, Carbopol, Carboxy vinyl Polymer.

Non proprietary names : B.P: carbomer U.S.P carbomeri

Chemical name : Carboxypolymethelene.

Structure :



Molecular weight : Carbomer resins are theoretically Estimated at $7x10^5$ to $4x10^9$.

Category : Emulsifying agent, suspending agent, tablet binder, viscosity- enhancing agent.

Description : Carbomers are white coloured, fully, Acidic, hygroscopic power with slightly characteristic odour.

Solubility : Soluble in water, and after neutralization, in ethanol (95%) and glycerine.

Viscosity : 29,000-39,000 cps (0.5%w/v),

Carbomers disperse in water to form acidic colloidal solutions of low. Viscosity when neutralized products highly viscous gels.

Stability and storage

Carbomers are stable, through hygroscopic materials and can be heated at temperatures below 104ºC for up to 2 hours without affecting their thickening efficacy. Dry powder forms of carbomers do not support the growth of moulds and fungi but aqueous dispersions are very susceptible to micro-organisms.

Safety

Carbomers are regulated as nontoxic and non-irritant material.

7. MATERIALS AND INSTRUMENTS

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MATERIALS

S.NO	MATERIALS	SOURCE	USES
1	Tadalafil	Sai mirra Inno pharm pvt ltd, Chennai.	Active pharmaceutical ingredient
2	Sorbitol	Keshavhi chem pvt ltd	Stabilizing agent
3	Propylene glycol	Prime laboratories pvt.ltd chennai	Polymer
4	Triethanolamine	AES manufacturing pvt,ltd chennai	Emulzifying agent
5	Carbopal	Alpha chemical pvt ltd chennai	Gel forming agent
6	Surcolose	Lowkal healthcare pvt ltd bengaluru	Sweetening agent
7	Sunset yellow	Sai mirra inno pharma pvt ltd chennai	Flavoring & coloring agent
8	Orange flavor	Sai mirra inno pharmap vt ltd chennai	Flavoring agent

EQUIPMENTS

S.NO	INSTRUMENTS	SOURCE
1	Electronic weighing balance	Percisa 205A.
2	Magnetic stirrer	Lasco.
3	pH meter	Elchem.
4	Viscosity	Viscometer
5	Dissolution test apparatus	Electro Lab dissolution apparatus.
6	UV-Spectrophotometry	Shimadzu.
7	FT-IR	IR Affinity-1, Shimadzu.
8	Sonicator	Saisonic Ultrasonic agitator.
9	HPLC	LC-2010 AHT, Shimadzu.
10	Stability chamber	InlabEquipments.

8. METHODLOGY

8.1 PREFORMULATION STUDIES

COMPATIBILITY STUDIES

Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and polymer was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 2 tons pressure. It was scanned from 4000 to 150 cm^{-1} in FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance of disappearance of peaks.

FORMULATION OF JELLY

- Propylene glycol to be warmed well.
- Tadalafil should be added to the above solution until the drug gets dissolved and cool it at room temperature.
- Carbopal 940 sieved at 100 # mesh and triethanolamine added and kept it for 30 mins and looks like jelly.
- Sucrulose dissolved in DM water and mixed to the jelly.
- Finally colouring and flavouring agents were added.
- This formulation was carried out with different formulation F1 –F6 whose quantity are given in the tabular column.

Formula

Table: 1

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Tadalafil	20	20	20	20	20	20
Sorbital	2200	2200	2200	2200	2200	2200
Propylene glycol	2715	2712.5	2710	2707.5	2705	2702.5
Carbapol 940	5	7.5	10	12.5	15	17.5
Triethanolamine	30	30	30	30	30	30
Sucrolose	30	30	30	30	30	30
Orange flavor	1ml	1ml	1ml	1ml	1ml	1ml
sunset yellow	1ml	1ml	1ml	1ml	1ml	1ml
Total	5000 mg	5000 mg	5000 mg	5000 mg	5000 mg	5000 mg

Evaluation of prepared oral jelly

Appearance

The prepared jelly was inspected visually for clarity, color and presence of any particulate materials. The test is important regarding patient compliance and acceptance.

Determination of pH

The pH values (Table 2) of 1% aqueous solutions of the prepared jellies were checked by using a calibrated digital pH meter (Elico India) at constant temperature. For the purpose 1g of the weighed formulation was dispersed in 100 ml of distilled water and the pH was noted. The standard pH of the jelly was 7.5-8.1.

Determination of Viscosity

Viscosity of the jelly was carried out by using (LV) Brookfield viscometer (Dial type). As the system is non-Newtonian spindle no. 4 was used. Viscosity was measured for the fixed time 2 min at 1.5rpm. Viscosity determination of jelly was done by Brookfield viscometer (Dial type).

Factor = 4 M

M = 1000

Viscosity = Dial reading x factor

The viscosity was calculated by following relation.

Viscosity in centipoises = Dial reading × Factor

The factor in above relation is found in factor finding chart provided by manufacturer of Brookfield viscometer.

DISSOLUTION

Apparatus	:	USP Apparatus II (paddle)
Medium	:	1000 mL of 0.5% SLS in water
RPM	:	100
Temperature	:	37°C ± 0.5°C
Time	:	45 minutes

Standard Preparation

Weigh accurately 20 mg standard of Tadalafil into a 100 mL volumetric flask. Dissolve in 10 mL Acetonitrile and dilute to volume with Acetonitrile and mix. Transfer 5 mL of this solution into a 100 mL volumetric flask and dilute to volume with dissolution medium and mix.

Sample preparation

Each jar containing 5gm of samplein 1000 mL dissolution medium that has been equilibrated to 37°C ± 0.5°C. Take care to exclude air bubbles from the surface of the tablets, start the apparatus immediately. Collect the sample after 45 minutes. Withdraw sample from a zone midway between the surface of the medium and top of the rotating blade and not less than 1 cm from the vessel wall and filter through Whatman No.1filter paper by discarding first 5 mL. Transfer 5 mL of this solution into a 10 mL volumetric flask and dilute to volume with dissolution medium and mix.

Procedure

Measure the absorbance of standard and sample preparations at 285 nm using dissolution medium as blank.

Calculation

$$\textbf{\% Label claim of Tadalafil dissolved} = \frac{\text{Test Abs.}}{\text{Std Abs.}} \times \frac{SW}{100} \times \frac{5}{100} \times \frac{1000}{20} \times \frac{10}{5} \times P$$

Where,

SW = Standard weight taken in mg

P = (%) Purity of Tadalafil Working Reference Standard

DRUG CONTENT ESTIMATION BY HPLC METHOD

Chromatographic conditions

Mobile phase: Buffer: Acetonitrile (70: 30)

[Buffer : Acetate Buffer pH 2.8 - Dissolve 4 g of anhydrous Sodium Acetate in about 840 ml of water, add sufficient Glacial Acetic Acid to adjust the pH to 2.8 (about 155 ml) and dilute to 1000 ml with water.]

Column: C18, 250 x 4.6 mm (NucleodurC18, 5µm is suitable)

Flow rate: 1.2 ml/min

Wave length: 283 nm

Temperature: Ambient

Load: 20 µl

Diluent: Water: Acetonitrile (1:1)

Standard preparation: Weigh accurately 20 mg of Tadalafil WRS into a 100 mL volumetric flask. Dissolve and dilute to volume with diluent.

Sample preparation: Weigh accurately5gm of sample (equivalent to about 20 mg of Tadalafil) into a 100 mL volumetric flask. Add 30 mL of diluent and sonicate for 30 minutes. Cool and dilute to volume with diluent. Mix well. Filter through 0.45 µ membrane filter by discarding the first 5 mL.

Procedure: Separately inject 6 replicate injections of standard preparation and the sample preparation into the liquid chromatography and record the peak area for major peaks.

System suitability: The relative standard deviation of six injections of standard preparation is not more than 2%. The tailing factor of Tadalafil peak is not more than 2.0.

Calculation: Calculate the content of Tadalafil present per tablet using the formula :

$$\text{Assay} = \frac{\text{Test Area}}{\text{Std.Area}} \times \frac{\text{Std. Wt.}}{100} \times \text{Dil.factor} \times \frac{100}{\text{Test Wt.}} \times \frac{\text{purity}}{100} \times \text{Avg Wt.}$$

Where,

Sw = Weight of Tadalafil working reference standard taken in mg

Tw = Test weight taken in g

Av.wt. = Average weight in g

P = (%) Purity of Tadalafil working reference Standard

Stability Studies at Various Temperatures

Stability studies of prepared jelly at different temperature condition were carried out with regards to temperature $4^{o}C$, $45^{o}C$ and at room temperature. The stability studies are carried out for 3 months and the formulations were analyzed for the changes in the physical parameters like appearance, pH, viscosity, sugar crystallization and stiffness at 15 days, 30 days, 60 days and 90 days.

KINETIC ANALYSIS OF *IN -VITRO* RELEASE RATES OF FORMULATIONS

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows

Zero-order kinetic model-cumulative percentage drug release versus time Korsmeyer's equation/peppa's model-log cumulative percentage drug released versus log

1. Zero-order kinetics

Zero order release would be predicted by the following equation:-

$$\mathbf{A_t = A_0 - K_0 t}$$

Where,

A_t = Drug release at time 't'

A_0 = Initial drug concentration

K_0 = Zero order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

2. First- order kinetics

First-order release would be predicted by the following equation:-

$$\mathbf{Log\ C = log\ C_0 - K_t /2.303}$$

Where,

C=Amount of drug remained at time 't'

C_0=Initial amount of drug

K=First-order rate constant (hr^{-1}

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant K can be obtained by multiplying 2.303 with slope values.

3. Higuchi's model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D\varepsilon / \tau(2A - \varepsilon Cs)\ Cst]^{1/2}$$

Where,

Q=Amount of drug released at time‘t’

D=Diffusion coefficient of drug in the matrix

A=Total amount of drug in unit volume of matrix

Cs= The solubility of drug in the matrix

ε= Porosity of the matrix

τ= Tortuosity

t= Time (hrs) at which Q amount of drug is released

Above equation may be simplified if one assumes that D, Cs, and A, are constant. Then equation becomes:

$$Q = K\ t^{½}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

4. Korsmeyer's equation/ peppa's model

To study the mechanism of drug release from the solid dispersions, the release data were also fitted to the well-known exponential equation (Korsmeyer's equation/peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$\mathbf{M_t/M_a = Kt^n}$$

Where,

M_t/M_a = The fraction of drug released at time't'

K= Constant incorporating the structural and geometrical characteristics of the drug/polymeric

N= Diffusion exponent related to the mechanism of release

Above equation can be simplified by applying log on both sides, and we get:

$$\mathbf{Log\ M_t/M_a = Log\ K + n\ Log\ t}$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y-intercept. For Fickian release 'n'=0.5 while for anomalous (non-Fickian) transport 'n' ranges from 0.5 to 1.0 as shown below.

Table: 2 Mechanism of drug release as per korsemeyer equation/peppa's model

S.No	n Value	Drug release
1.	n < 0.5	Fickian release
2.	0.5<n<1	Non- Fickian release
3.	n>1	Case II transport

9.RESULTS

Tadalafil oral jellies were prepared and evaluated to increase its local action and bioavailability. In the present study 6 formulations with variable concentration of polymer were prepared and evaluated for it physio -chemical, *in-vitro* drug release studies.

PREFORMULATION STUDIES

COMPATIBILITY STUDIES [FTIR]

Compatibility studies were performed using FTIR spectrophotometer. The IR spectrum of pure drug and polymer were studied. The characteristic absorption peaks of Tadalafil were obtained at the peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. That indicates the drug was compatible with the excipients.

Peak	Wave length cm-1
N - H Stretching	3387.11
C - H Stretching	2970.48
C = O Stretching	1716.70
C = C Stretching	1452.45
N - CH3 Stretching	2300.01

TADALAFIL STANDARD - FTIR

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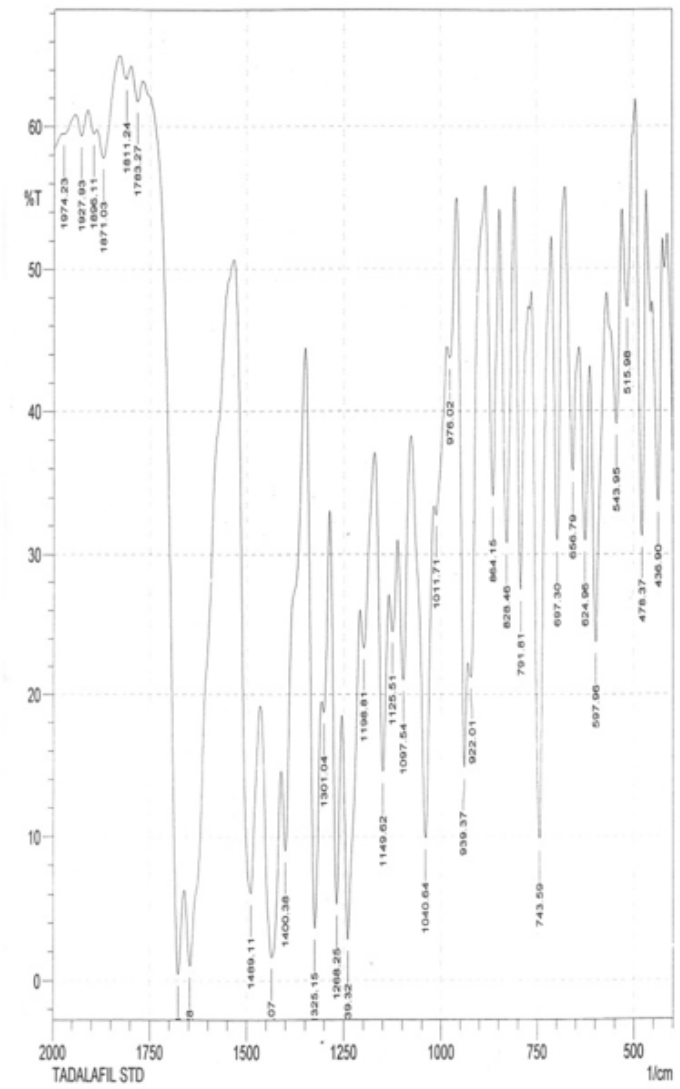

No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	436.9	33.676	16.419	451.36	425.32	10.218	2.352
2	478.37	31.235	26.519	494.76	467.76	10.011	3.676
3	515.98	47.261	9.763	528.52	495.73	9.037	1.256
4	543.95	39.088	12.85	568.06	529.48	13.539	2.316
5	597.96	23.69	21.053	611.46	569.03	19.24	4.801
6	624.96	30.969	12.851	639.43	612.43	11.714	2.043
7	656.79	35.815	13.836	676.08	640.39	13.214	2.36
8	697.3	30.956	22.637	710.8	677.04	12.485	3.446
9	743.59	9.826	40.049	762.88	711.76	28.036	12.805
10	791.81	27.445	24.662	806.28	771.56	14.052	3.94
11	828.46	30.815	24.055	845.82	807.24	14.806	4.781
12	864.15	34.118	20.905	882.47	846.79	12.958	3.698
13	922.01	21.212	6.647	929.73	883.44	19.592	0.92
14	939.37	14.8	17.924	957.7	930.69	15.436	3.018
15	976.02	43.758	3.711	982.77	958.66	7.839	0.525
16	1011.71	32.74	2.581	1017.49	983.74	14.544	0.653
17	1040.64	9.94	25.291	1076.33	1018.46	37.626	11.723
18	1097.54	20.99	12.918	1111.05	1077.29	18.7	3.125
19	1125.51	24.463	4.193	1134.19	1112.01	12.754	0.862
20	1149.62	14.525	16.719	1169.88	1135.16	22.511	5.116
21	1198.81	23.271	5.608	1208.46	1170.84	20.363	1.381
22	1239.32	2.838	18.166	1254.75	1209.42	44.612	14.776
23	1268.25	5.305	19.244	1285.61	1255.71	26.313	8.026
24	1301.04	18.698	4.684	1306.83	1286.58	12.902	0.979
25	1325.15	3.623	26.522	1348.3	1307.79	35.14	13.448
26	1400.38	6.994	10.689	1410.99	1349.26	39.636	3.611
27	1436.07	1.605	15.064	1465	1411.95	65.246	23.988
28	1489.11	6.083	23.895	1533.47	1465.96	52.555	18.392
29	1647.28	1.012	10.72	1661.75	1546.98	95.336	15.418
30	1677.18	0.442	13.563	1769.76	1662.71	67.453	13.075
31	1783.27	61.751	1.936	1799.66	1770.73	5.864	0.204
32	1811.24	63.358	1.206	1827.63	1800.63	5.241	0.122
33	1871.03	57.784	3.574	1888.39	1831.49	12.37	0.701
34	1896.11	59.476	0.707	1911.54	1889.36	4.914	0.06
35	1927.93	59.309	1.676	1944.33	1912.5	7.024	0.189
36	1974.23	59.461	0.048	1975.19	1945.29	6.61	0.016

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CARBOPOL – 940P STANDARD - FTIR

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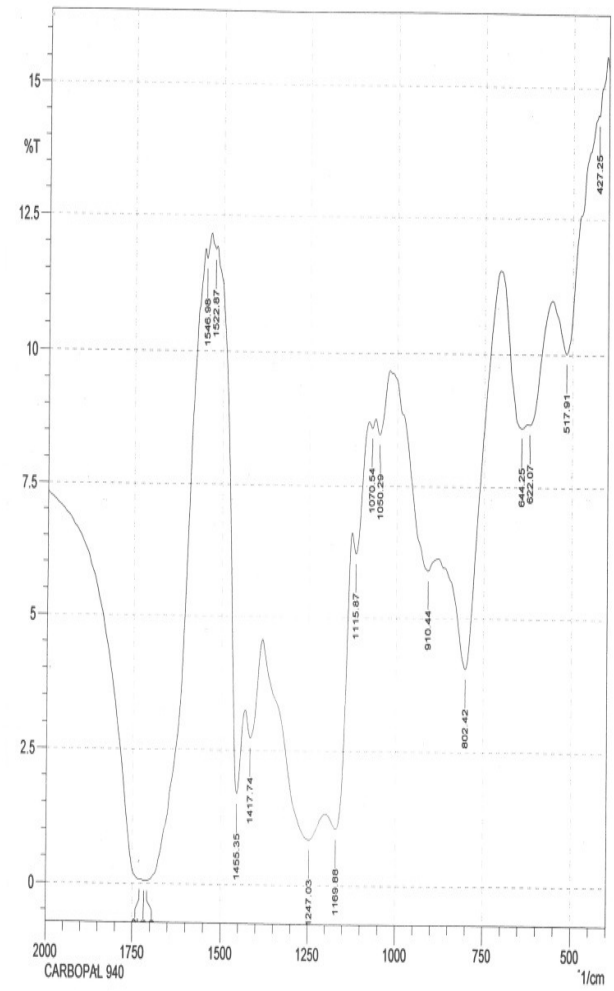

No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	427.25	14.47	0.106	429.18	405.07	19.866	0.044
2	517.91	10.022	2.052	557.45	430.14	118.267	3.876
3	622.07	8.685	0.202	627.86	558.42	70.287	0.431
4	644.25	8.617	0.653	705.01	628.82	77.587	1.492
5	802.42	4.054	4.469	879.58	705.98	205.9	19.348
6	910.44	5.892	0.988	1021.35	880.54	159.604	3.417
7	1050.29	8.472	0.549	1060.89	1022.32	40.506	0.581
8	1070.54	8.592	0.15	1079.22	1061.86	18.441	0.068
9	1115.87	6.207	0.846	1125.51	1080.18	51.767	1.133
10	1169.88	1.057	2.427	1199.78	1126.48	125.825	14.298
11	1247.03	0.853	1.301	1383.02	1200.74	319.393	26.041
12	1417.74	2.733	0.896	1431.24	1383.98	69.883	3.153
13	1455.35	1.687	3.903	1518.04	1432.21	109.897	9.149
14	1522.87	11.858	0.116	1534.44	1519.01	14.237	0.042
15	1546.98	11.687	0.261	1551.8	1535.4	15.169	0.081
16	1709	0.053	0.291	1712.86	1552.76	284.249	0.946
17	1717.68	0.054	0.012	1726.36	1713.83	40.263	0.528
18	1730.22	0.079	0.078	2000.27	1727.33	406.203	0.201

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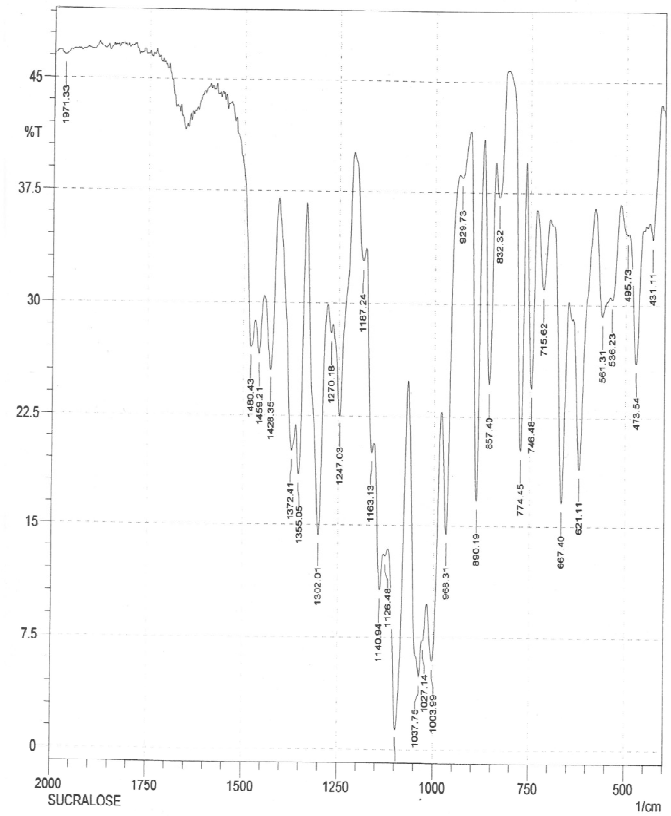

No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	431.11	34.41	2.99	437.86	409.89	11.806	0.506
2	473.54	26.114	8.734	491.87	456.18	18.34	2.003
3	495.73	34.656	0.356	514.05	492.83	9.59	0.094
4	536.23	30.36	1.384	541.06	515.02	12.642	0.336
5	561.31	29.252	4.334	578.63	542.02	19.048	1.089
6	621.11	18.919	12.309	637.5	580.6	32.028	4.364
7	667.4	16.608	15.973	686.69	650.04	22.577	4.711
8	715.62	31.021	5.022	732.02	699.23	15.591	1.055
9	746.48	24.429	13.466	760.95	732.98	14.421	2.624
10	774.45	20.148	20.958	808.21	761.91	21.529	4.385
11	832.32	37.166	4.062	841	809.17	12.484	0.743
12	857.4	24.687	15.637	871.86	841.96	15.041	3.23
13	890.19	16.716	24.662	907.55	872.83	19.134	5.825
14	929.73	38.489	0.921	936.48	908.51	11.239	0.173
15	968.31	14.441	12.943	980.84	937.44	25.883	3.449
16	1003.99	5.929	8.793	1017.49	981.81	35.331	6.07
17	1027.14	7.28	0.477	1029.07	1018.46	11.475	0.152
18	1037.75	4.916	5.996	1067.65	1030.03	38.876	5.932
19	1098.51	1.377	16.667	1118.76	1068.61	56.794	19.896
20	1126.48	12.933	0.261	1130.33	1119.73	9.362	0.053
21	1140.94	10.611	5.361	1156.37	1131.3	21.572	1.828
22	1163.13	19.943	4.111	1179.52	1157.34	13.781	0.882
23	1187.24	32.818	2.265	1211.35	1180.49	13.744	0.368
24	1247.03	22.466	10.102	1265.36	1212.31	28.529	3.674
25	1270.18	28.042	0.916	1279.82	1266.32	7.318	0.096
26	1302.01	14.325	18.198	1334.8	1280.79	34.768	8.777
27	1355.05	18.461	7.259	1361.8	1335.76	15.96	1.823
28	1372.41	20.075	4.989	1408.1	1362.77	26.083	1.335
29	1428.35	25.571	8.023	1445.71	1409.06	19.357	2.043
30	1459.21	26.56	3.036	1469.82	1446.67	12.698	0.489
31	1480.43	27.088	4.854	1504.54	1470.79	16.718	0.848
32	1971.33	46.551	0.141	1976.16	1956.87	6.388	0.022

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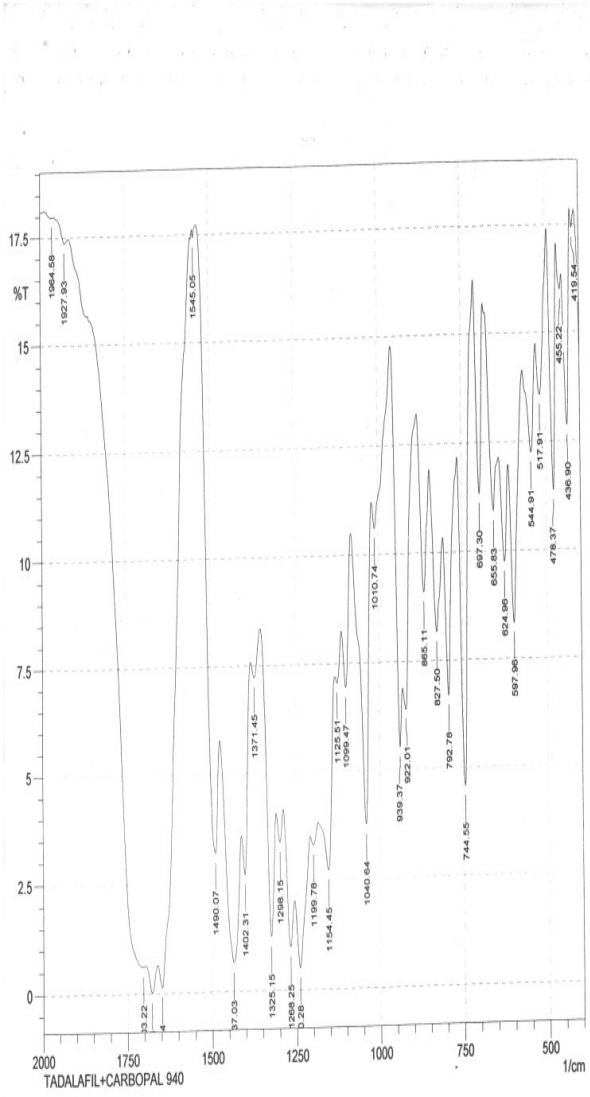
TADALAFIL + CARBOPOL 940P - FTIR



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	419.54	17.406	0.436	424.36	412.78	8.73	0.067
2	436.9	12.849	4.348	451.36	425.32	21.696	1.738
3	455.22	15.987	0.456	465.83	452.33	10.665	0.145
4	478.37	11.373	5.838	493.8	466.79	23.171	2.547
5	517.91	13.564	2.059	529.48	494.76	28.751	1.161
6	544.91	12.249	1.932	559.38	530.45	25.52	0.982
7	597.96	8.323	4.384	612.43	569.03	41.643	3.256
8	624.96	9.739	2.31	639.43	613.39	25.188	1.261
9	655.83	10.916	2.605	678.01	640.39	34.055	1.566
10	697.3	11.328	4.616	710.8	683.79	23.668	2.126
11	744.55	4.562	9.08	762.88	711.76	51.906	8.432
12	792.78	6.68	4.262	807.24	763.84	44.562	3.342
13	827.5	8.164	2.965	846.79	808.21	39.439	2.578
14	865.11	9.094	3.436	882.47	847.75	33.824	2.463
15	922.01	6.383	1.537	929.73	883.44	46.655	0.884
16	939.37	5.502	3.748	959.63	930.69	30.865	2.071
17	1010.74	10.601	1.084	1018.46	960.59	52.909	1.439
18	1040.64	3.756	7.214	1081.15	1019.42	70.348	10.833
19	1099.47	6.934	2.215	1111.05	1082.11	31.488	1.703
20	1125.51	7.045	0.466	1131.3	1112.01	21.784	0.341
21	1154.45	2.722	3.035	1184.34	1132.26	73.377	6.842
22	1199.78	3.303	0.318	1208.46	1185.31	33.762	0.526
23	1240.28	0.497	2.027	1255.71	1209.42	84.634	11.897
24	1268.25	0.98	1.852	1287.54	1256.68	53.38	5.839
25	1298.15	3.387	0.713	1308.76	1288.5	29.006	0.91
26	1325.15	1.229	4.387	1352.16	1309.72	61.871	9.409
27	1371.45	7.221	0.642	1382.06	1353.12	32.343	0.56
28	1402.31	2.662	2.228	1411.95	1383.02	39.801	2.85
29	1437.03	0.648	3.773	1474.64	1412.92	106.294	23.244
30	1490.07	3.174	5.489	1535.4	1475.61	68.239	9.26
31	1545.05	17.422	0.195	1546.98	1536.37	8.005	0.017
32	1648.24	0.135	2.484	1660.78	1553.73	151.132	9.175
33	1678.14	0.017	0.632	1696.47	1661.75	91.01	15.042
34	1703.22	0.605	0.014	1705.15	1697.43	17.057	0.059
35	1927.93	17.362	0.267	1955.9	1915.4	30.519	0.087
36	1964.58	17.978	0.035	1981.94	1960.73	15.793	0.02

Comment;
TADALAFIL+CARBOPAL 940

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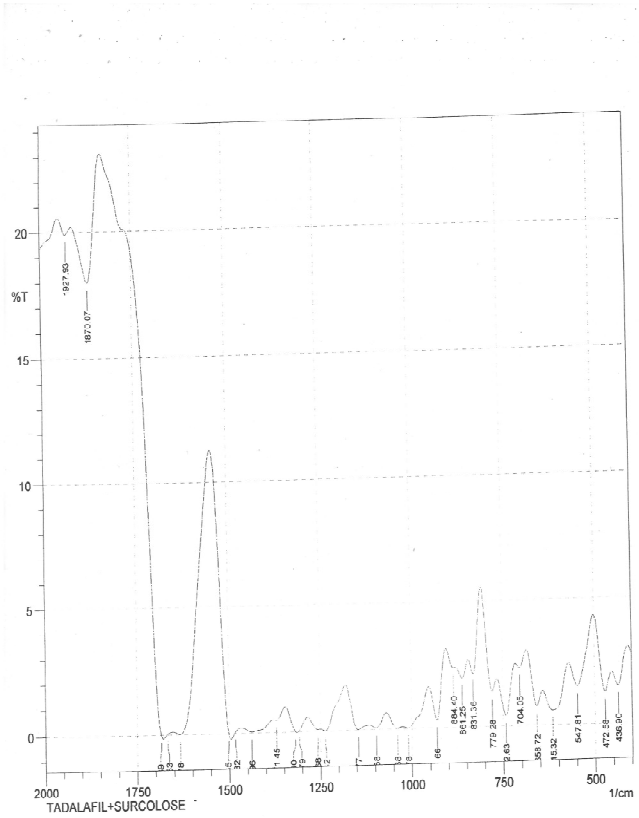
Resolution;
Apodization;
User; A

TADALAFIL + SUCRALOSE - FTIR



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	436.9	1.469	0.951	453.29	409.89	73.564	4.076
2	472.58	1.246	1.67	501.51	454.26	79.115	6.791
3	547.81	1.482	1.58	570.95	502.48	111.668	9.725
4	615.32	0.57	1.2	642.32	571.92	141.244	18.819
5	658.72	0.751	1.211	684.76	643.29	77.22	6.753
6	704.05	2.281	0.367	714.66	685.72	46.263	0.953
7	742.63	0.421	1.71	765.77	715.62	97.729	13.99
8	779.28	1.376	1.643	806.28	766.74	64.252	5.04
9	831.36	2.103	1.533	843.89	807.24	55.402	3.662
10	861.25	1.923	0.587	878.61	844.86	55.984	1.939
11	884.4	2.345	0.162	904.65	879.58	39.796	0.478
12	931.66	0.305	1.988	952.88	905.62	92.548	14.8
13	1009.78	0.02	0.371	1024.25	953.84	182.814	11.414
14	1039.68	0.025	0.24	1068.61	1025.21	127.208	11.741
15	1096.58	0.055	0.307	1115.87	1069.57	127.461	12.415
16	1145.77	0.006	0.894	1179.52	1116.83	171.819	29.109
17	1236.42	0.004	0.393	1249.93	1180.49	174.312	13.124
18	1256.68	0.058	0.005	1284.65	1250.89	93.529	2.695
19	1307.79	0.025	0.022	1308.76	1285.61	59.339	0
20	1318.4	0	0	1319.37	1317.44	385.78	94.592
21	1371.45	0.476	0.152	1380.13	1347.34	72.18	1.742
22	1438.96	0.036	0.254	1465.96	1381.09	244.901	32.252
23	1483.32	0.037	0.009	1484.29	1466.93	49.384	0
24	1501.85	0	0	1502.61	1500.68	385.78	94.946
25	1633.78	0.013	2.063	1653.07	1544.08	212.907	19.016
26	1667.53	0.018	0.006	1668.5	1654.03	45.156	0
27	1684.89	0	-0.021	1685.86	1683.93	385.78	94.739
28	1870.07	17.983	3.719	1911.54	1831.49	56.38	3.132
29	1927.93	19.901	0.442	1949.15	1912.5	25.508	0.182

Comment;
TADALAFIL+SURCOLOSE

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Resolution;
Apodization;
User; A

Physical properties of the oral jelly formulations

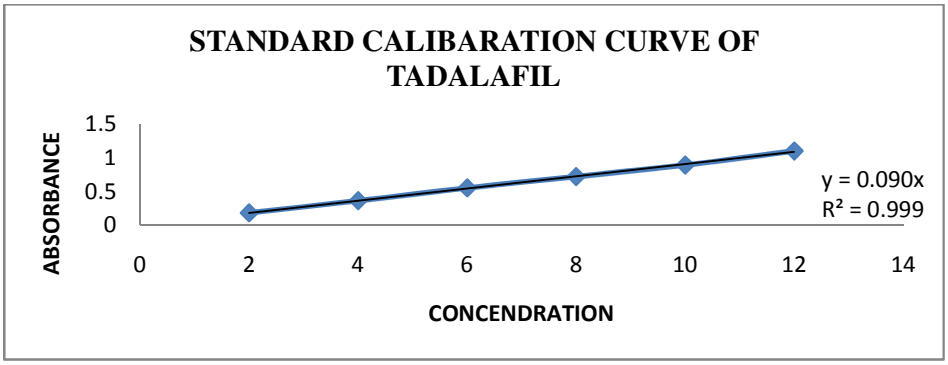
Table: 3

Formulations	Appearance	pH	Taste	Viscosity (cps)*
F1	Transparent	7.5	Bitter	273600
F2	Transparent	7.6	Bitter	351234
F3	Opaque	7.0	Bitter	542335
F4	Opaque	7.6	Bitter	335435
F5	Opaque	8.1	Bitter	294520
F6	Transparent	7.7	Bitter	482355

STANDARD CALIBRATION CURVE OF TADALAFIL

Standard calibration curve of tadalafil was determined by plotting absorbance vs concentration at 285nm and it follows the beers law. the results were show in table

	CONCENTRATION	ABSORBANCE
1	2	0.18
2	4	0.36
3	6	0.55
4	8	0.72
5	10	0.89
6	12	1.1



DISSOLUTION STUDIES

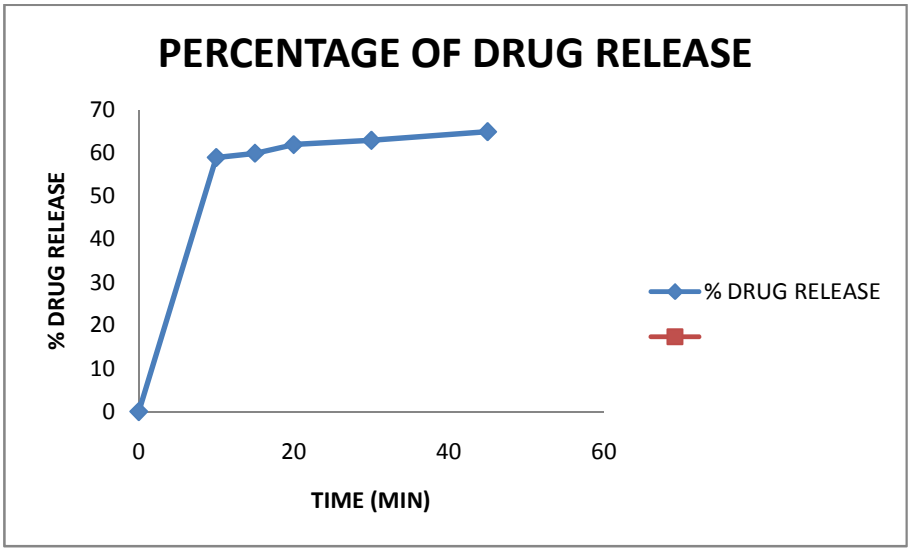
FORMULATION 1

PERCENTAGE OF DRUG RELEASE

Table: 4

S. No	Times in (mins)	Absorbance (nm)	concentration	Amount of drug release (mg)	Amount of drug release mg/1000	Cumulative of % drug release	% drug release
1	10	0.215	1.17	0.011	11.7	11.72	59.50%
2	15	0.217	1.18	0.11	11.8	11.83	60%
3	20	0.225	1.22	0.12	12.2	12.26	62.2%
4	30	0.230	1.25	0.12	12.5	12.53	63.6%
5	45	0.234	1.27	0.12	12.7	12.75	64.7%

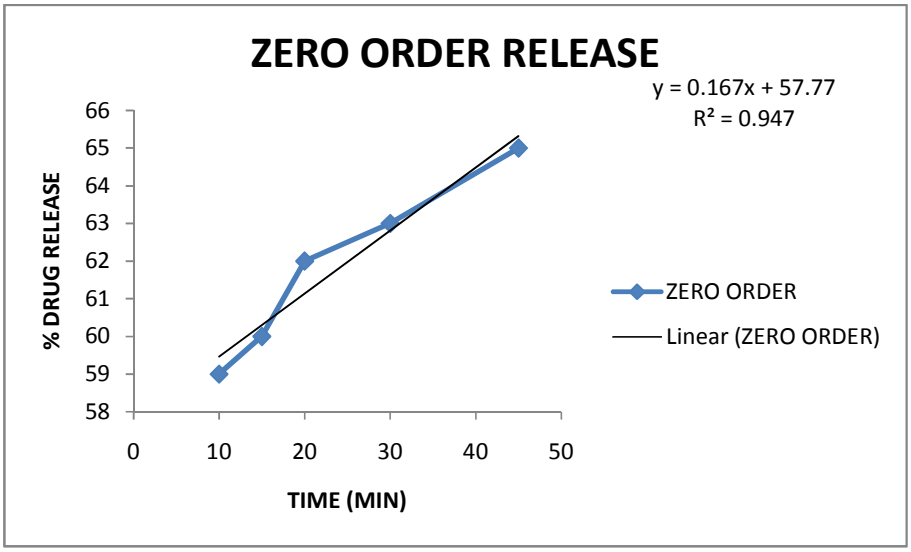
IN-VITRO DRUG RELEASE STUDIES FOR FORMULATION F1

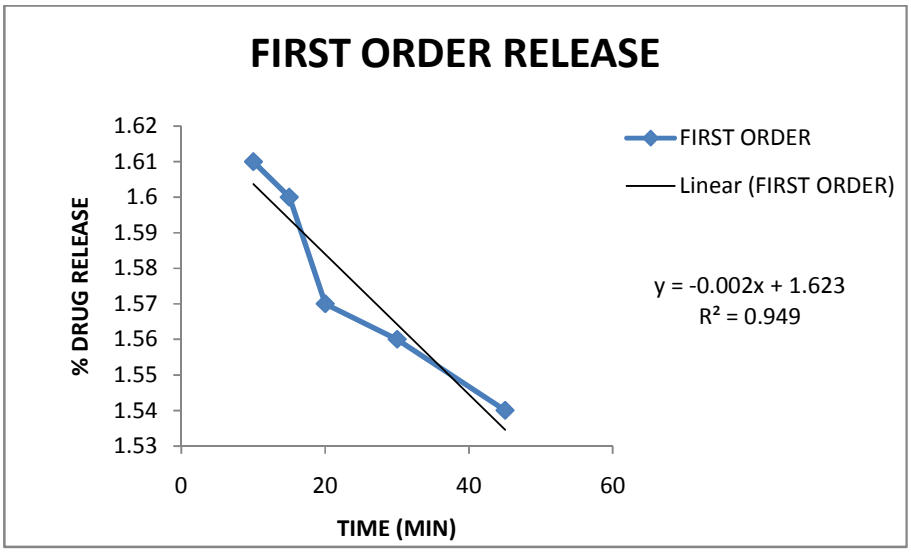


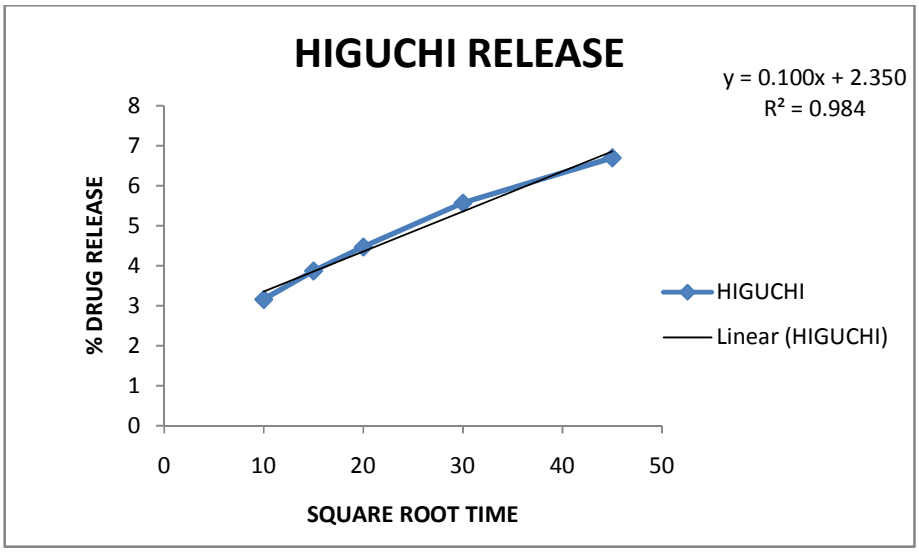
KINETICS OF DRUG RELEASE:

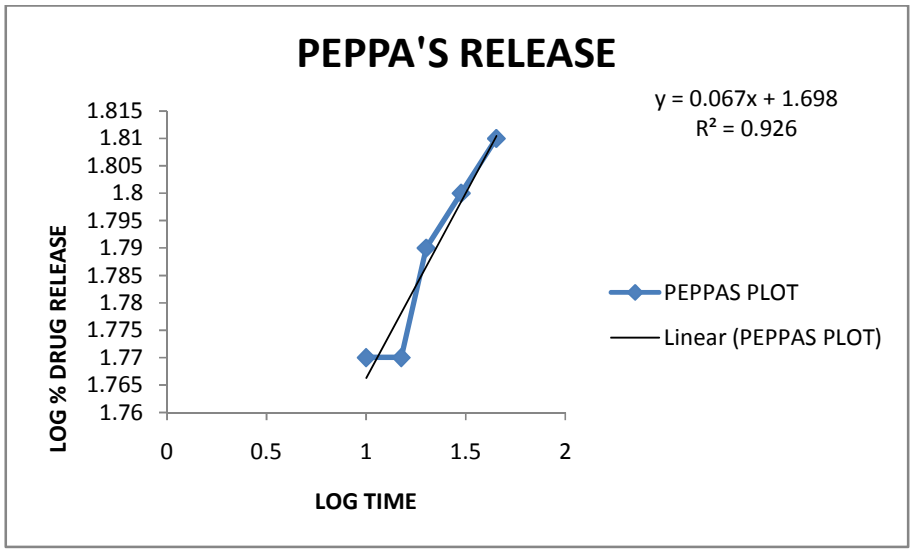
Table: 5

S.NO	Time in Mins	Square root of time	log time	% drug release	log % drug release	% drug remaining	Log % drug remaining
1	10	3.162	1	59	1.770	41	1.612
2	15	3.872	1.17	60.1	1.778	39.9	1.600
3	20	4.47	1.30	62.4	1.795	37.6	1.575
4	30	5.47	1.47	63.5	1.802	36.5	1.562
5	45	6.70	1.65	65.1	1.810	34.9	1.542




FIRST ORDER RELEASE
% DRUG RELEASE
1.62
1.61
1.6
1.59
1.58
1.57
1.56
1.55
1.54
1.53
0
20
40
60
TIME (MIN)
FIRST ORDER
Linear (FIRST ORDER)
y = -0.002x + 1.623
R² = 0.949


HIGUCHI RELEASE
% DRUG RELEASE
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
SQUARE ROOT TIME
y = 0.100x + 2.350
R² = 0.984
HIGUCHI
Linear (HIGUCHI)

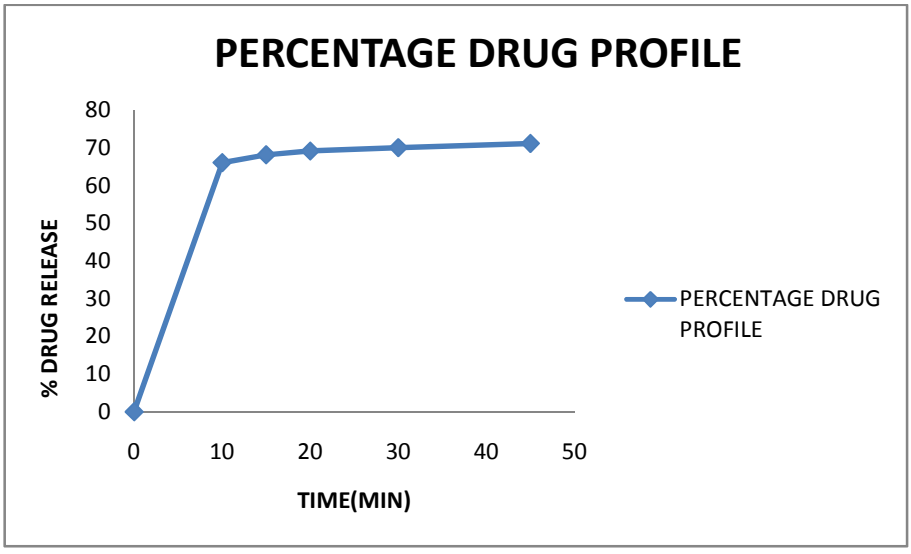


FORMULATION 2

Table: 6

S.NO	Times in (mins)	Absorbance (nm)	concentration	Amount of drug release (mg)	Amount of drug release mg/1000	Cumulative of % drug release	% drug release
1	10	0.236	1.318	0.013	13.18	13.19	66.99
2	15	0.242	1.351	0.013	13.51	13.53	68.6
3	20	0.245	1.368	0.013	13.68	13.70	69.5
4	30	0.248	1.386	0.013	13.85	13.86	70.3
5	45	0.253	1.413	0.014	14.13	14.14	71.8

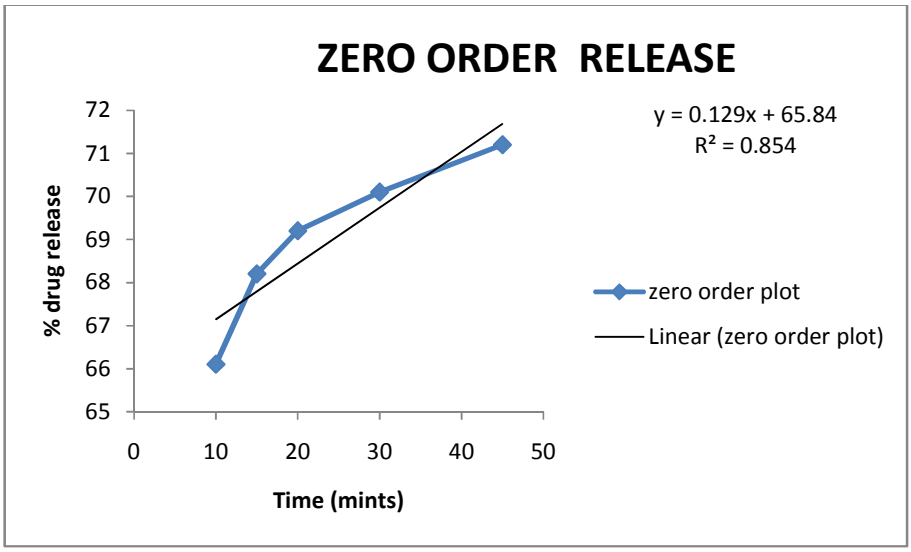
\



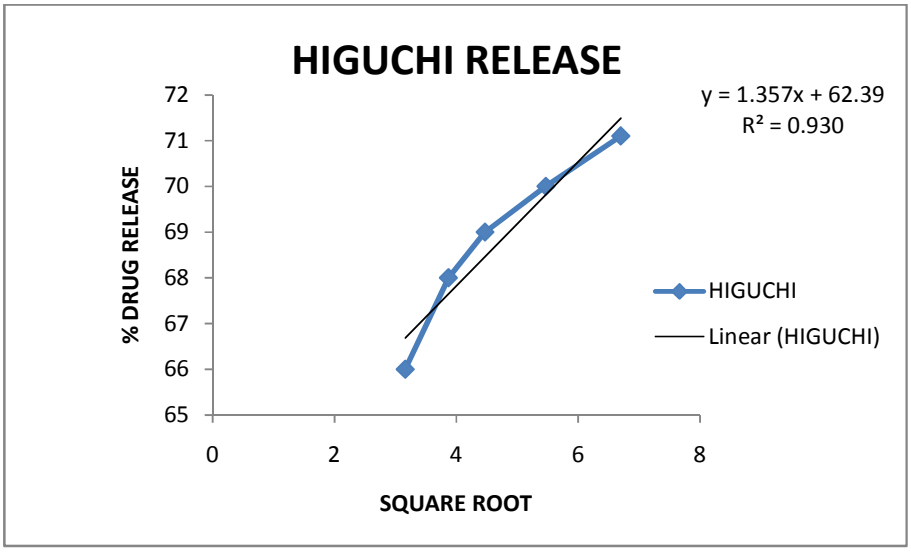
KINETICS OF DRUG RELEASE:

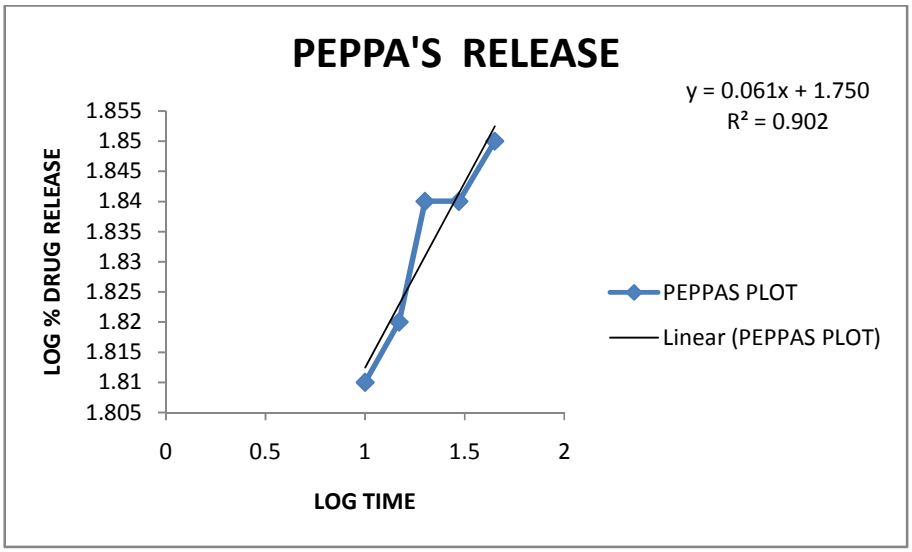
Table: 7

S.NO	Time in Mins	Square root of time	log time	% drug release	log % drug release	% drug remaining	Log % drug remaining
1	10	3.163	1.12	66.9	1.819	34	1.53
2	15	3.87	1.17	68.6	1.83	32	1.50
3	20	4.47	1.30	69.5	1.83	31	1.49
4	30	5.47	1.47	70.3	1.84	30	1.47
5	45	6.47	1.65	71.8	1.85	28.2	1.45




FIRST ORDER RELEASE
1.54
1.52
1.5
1.48
1.46
1.44
1.42
log % drug remaing
0
20
40
60
time (mints)
y = -0.002x + 1.538
R² = 0.909
FIRST ORDER
Linear (FIRST ORDER)

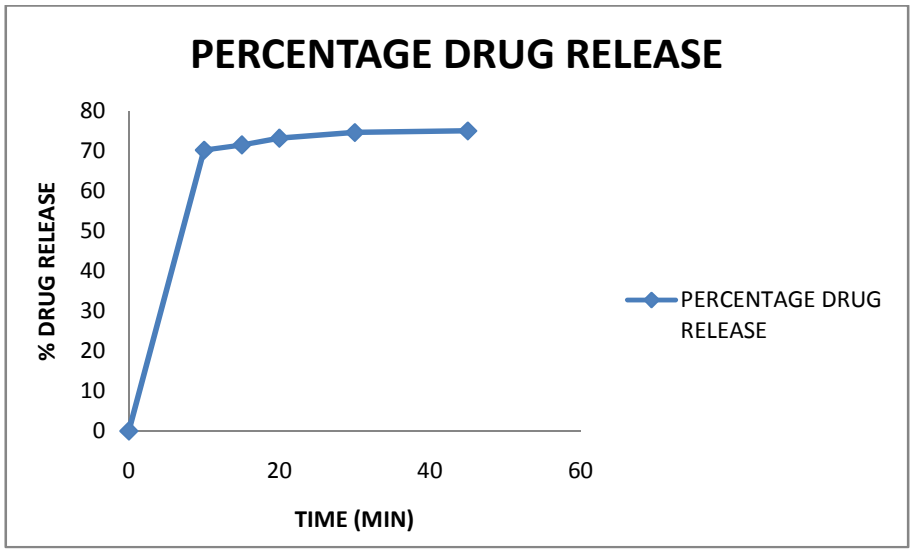

HIGUCHI RELEASE
72
71
70
69
68
67
66
65
% DRUG RELEASE
0
2
4
6
8
SQUARE ROOT
y = 1.357x + 62.39
R² = 0.930
HIGUCHI
Linear (HIGUCHI)


PEPPA'S RELEASE
y = 0.061x + 1.750
R² = 0.902
LOG % DRUG RELEASE
1.855
1.85
1.845
1.84
1.835
1.83
1.825
1.82
1.815
1.81
1.805
0
0.5
1
1.5
2
LOG TIME
PEPPAS PLOT
Linear (PEPPAS PLOT)

FORMULATION 3

Table: 8

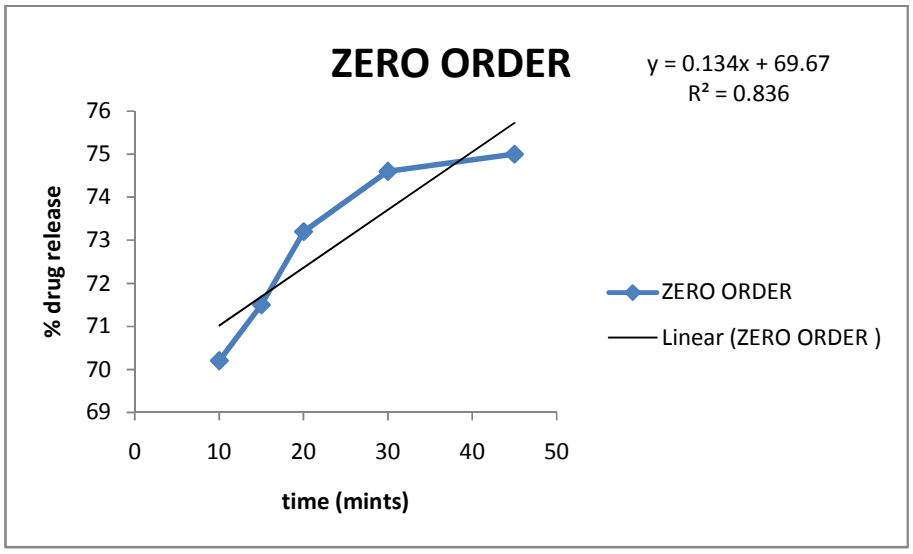
S.NO	Times in (mins)	Absorbance (nm)	concentration	Amount of drug release (mg)	Amount of drug release mg/1000	Cumulative of % drug release	% drug release
1	10	0.254	1.383	0.013	13.83	13.34	70.29
2	15	0.259	1.41	0.014	14.10	14.12	71.63
3	20	0.262	1.42	0.014	14.27	14.28	72.50
4	30	0.266	1.44	0.014	14.48	14.56	73.61
5	45	0.271	1.47	0.014	14.76	14.75	75.0

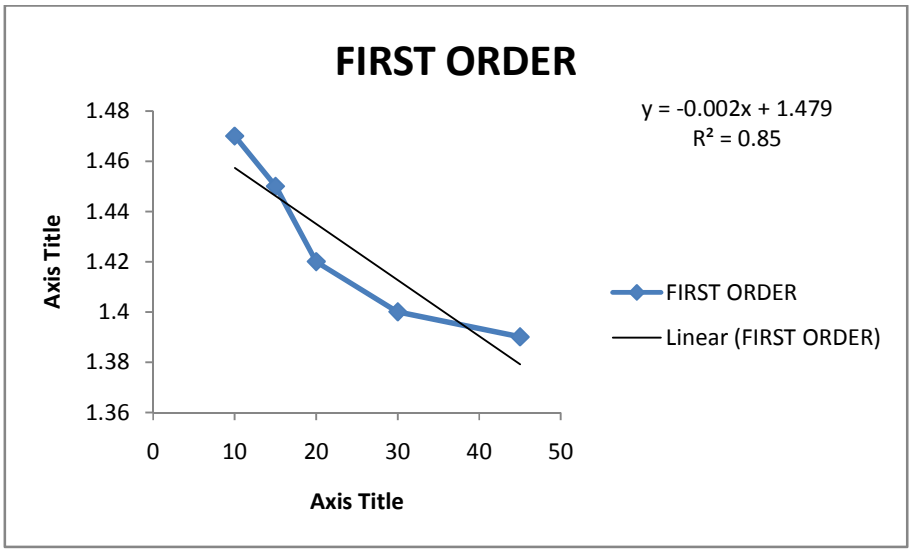


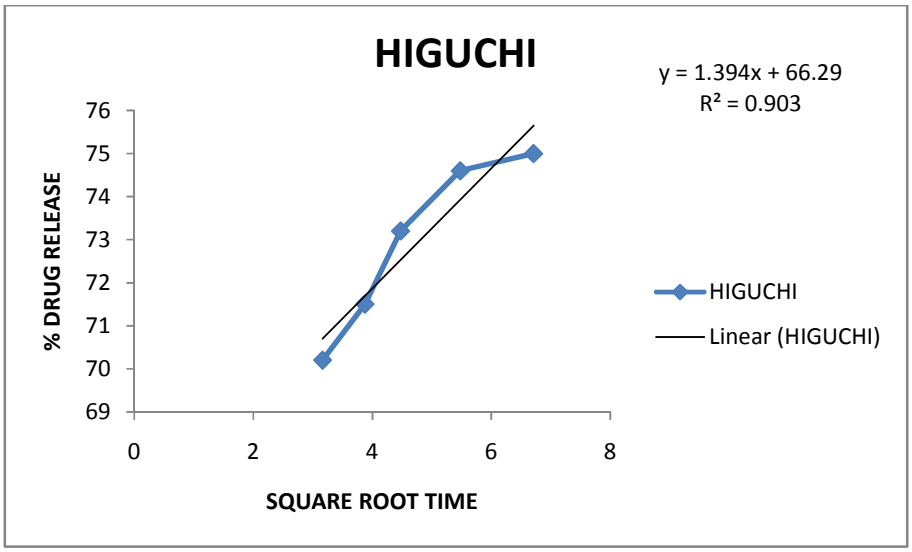
KINETICS OF DRUG RELEASE:

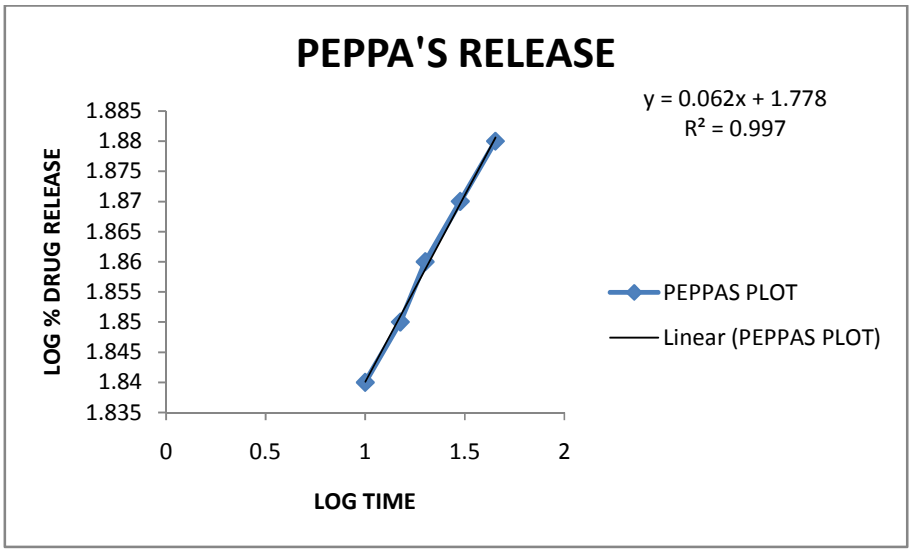
Table: 9

S.NO	Time in Mins	Square root of time	log time	% drug release	log % drug release	% drug remaining	Log % drug remaining
1	10	3.162	1	70.2	1.846	29.8	1.474
2	15	3.87	1.17	71.5	1.854	28.5	1.484
3	20	4.47	1.30	73.2	1.864	26.8	1.428
4	30	5.47	1.47	74.6	1.872	25.4	1.404
5	45	6.70	1.65	75	1.875	25	1.397




FIRST ORDER
y = -0.002x + 1.479
R² = 0.85
1.48
1.46
1.44
1.42
1.4
1.38
1.36
Axis Title
0
10
20
30
40
50
Axis Title
FIRST ORDER
Linear (FIRST ORDER)

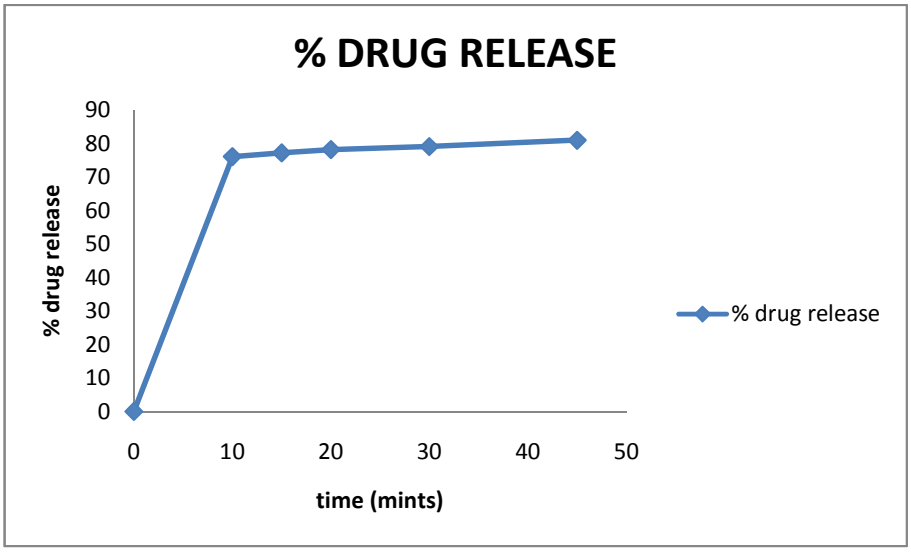

HIGUCHI
y = 1.394x + 66.29
R² = 0.903
76
75
74
73
72
71
70
69
% DRUG RELEASE
0
2
4
6
8
SQUARE ROOT TIME
HIGUCHI
Linear (HIGUCHI)



FORMULATION 4

Table: 10

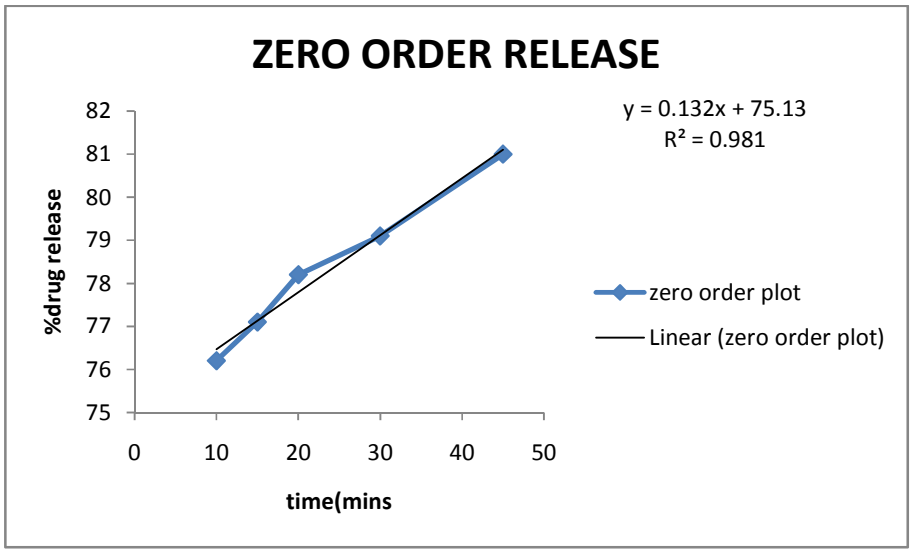
S.NO	Times in (mins)	Absorbance (nm)	concentration	Amount of drug release (mg)	Amount of drug release mg/1000	Cumulative of % drug release	% drug release
1	10	0.275	1.497	0.014	14.97	14.99	76.1
2	15	0.279	1.51	0.015	15.19	15.21	77.2
3	20	0.283	1.54	0.015	15.41	15.42	78.3
4	30	0.286	1.55	0.015	15.57	15.59	79.1
5	45	0.293	1.59	0.015	15.95	15.97	81.0



KINETICS OF DRUG RELEASE:

Table: 11

S.NO	Time in Mins	Square root of time	log time	% drug release	log % drug release	% drug remaining	Log % drug remaining
1	10	3.16	1	76.2	1.88	23.8	1.376
2	15	3.87	1.17	77.1	1.88	22.9	1.359
3	20	4.47	1.30	78.2	1.89	21.8	1.338
4	30	5.47	1.47	79.1	1.89	20.9	1.320
5	45	6.47	1.65	81	1.90	19	1.278



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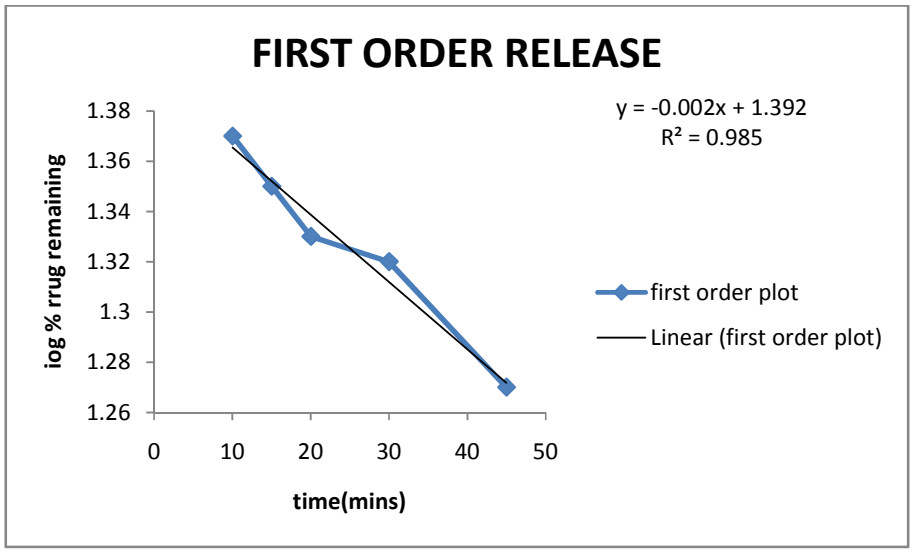
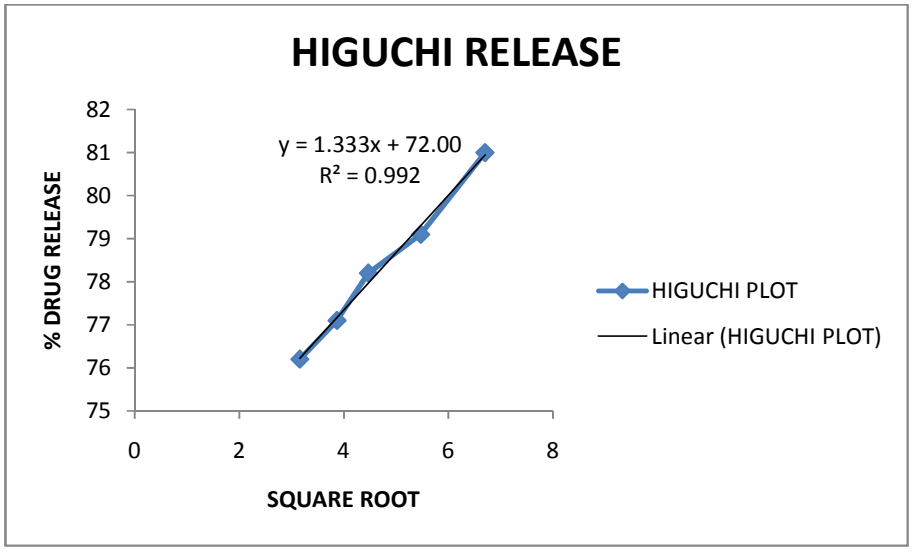
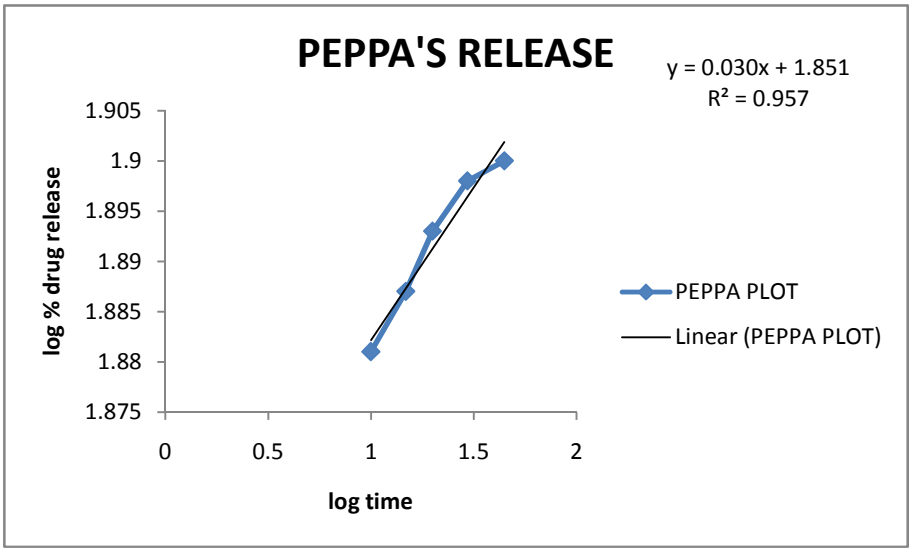

FIRST ORDER RELEASE
y = -0.002x + 1.392
R² = 0.985
iog % rrug remaining
1.38
1.36
1.34
1.32
1.3
1.28
1.26
0
10
20
30
40
50
time(mins)
first order plot
Linear (first order plot)

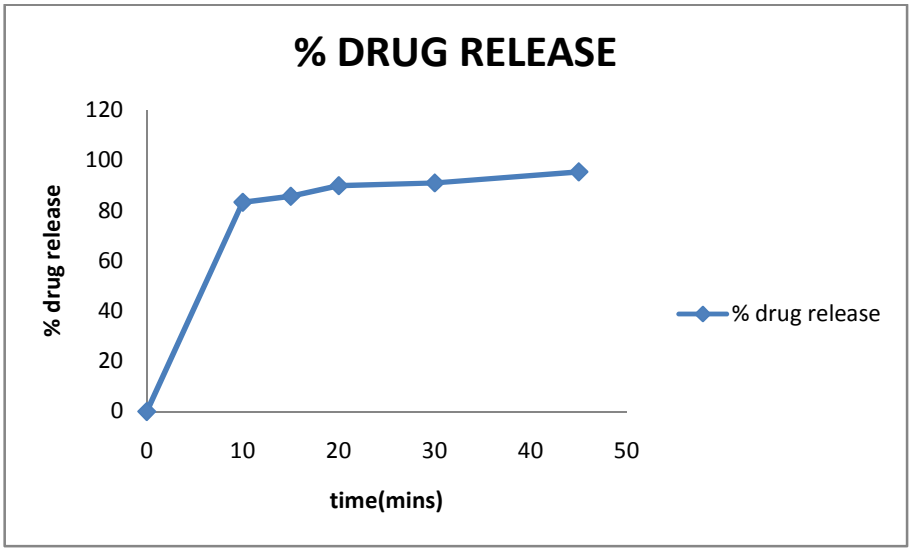

HIGUCHI RELEASE
y = 1.333x + 72.00
R² = 0.992
% DRUG RELEASE
82
81
80
79
78
77
76
75
0
2
4
6
8
SQUARE ROOT
HIGUCHI PLOT
Linear (HIGUCHI PLOT)



FORMULATION 5

Table: 12

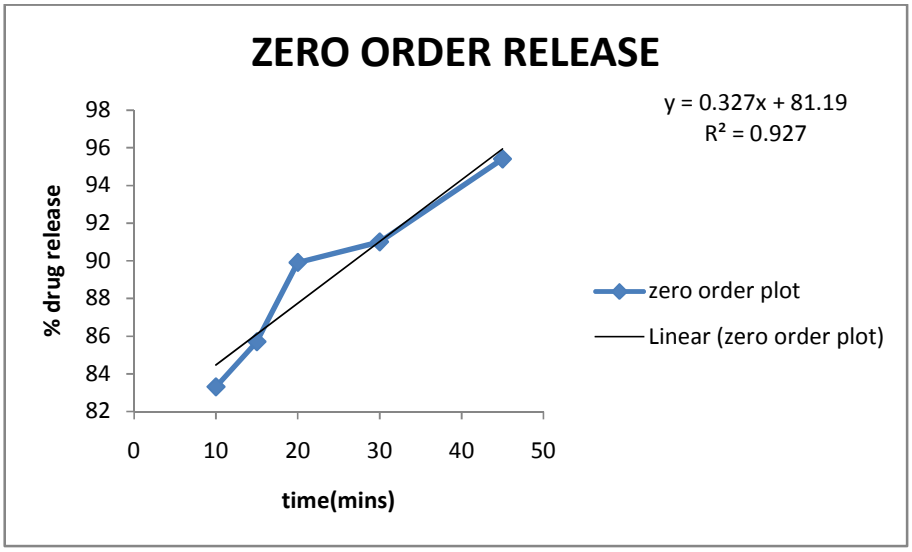
S.NO	Times in (mins)	Absorbance (nm)	concentration	Amount of drug release (mg)	Amount of drug release mg/1000	Cumulative of % drug release	% drug release
1	10	0.301	1.639	0.016	16.39	16.41	83.3
2	15	0.310	1.688	0.016	16.84	16.90	85.7
3	20	0.325	1.77	0.017	17.70	17.71	89.9
4	30	0.329	1.79	0.017	17.91	17.93	91.0
5	45	0.345	1.87	0.018	18.79	18.80	95.4

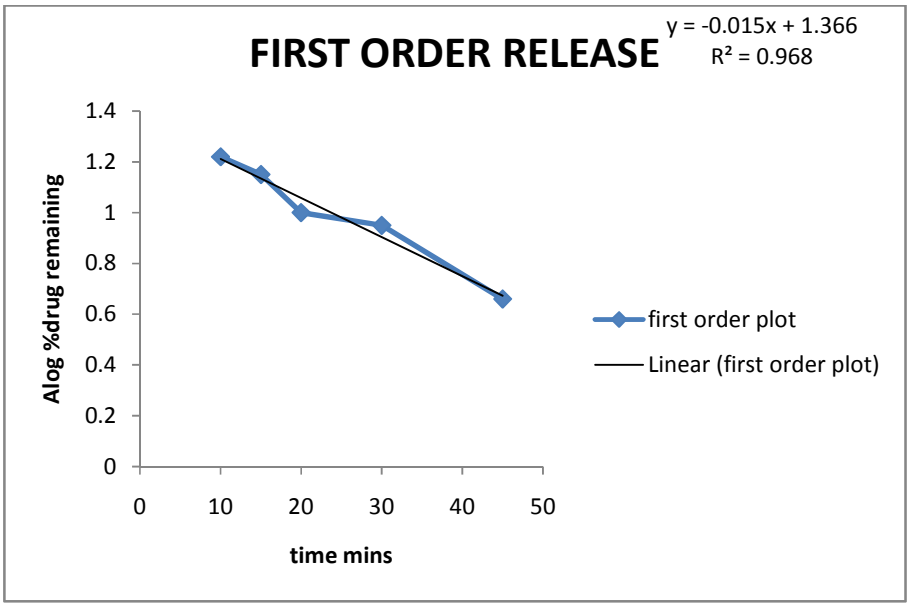


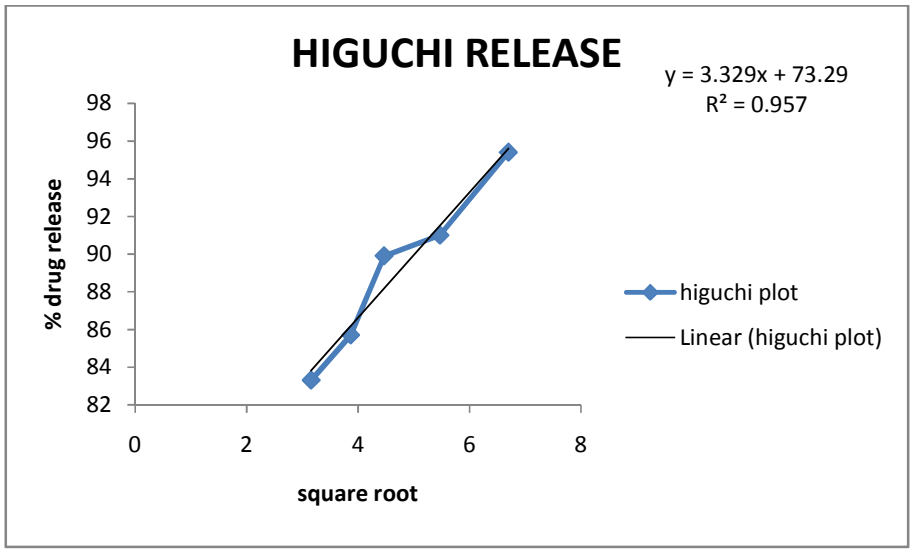
KINETICS OF DRUG RELEASE:

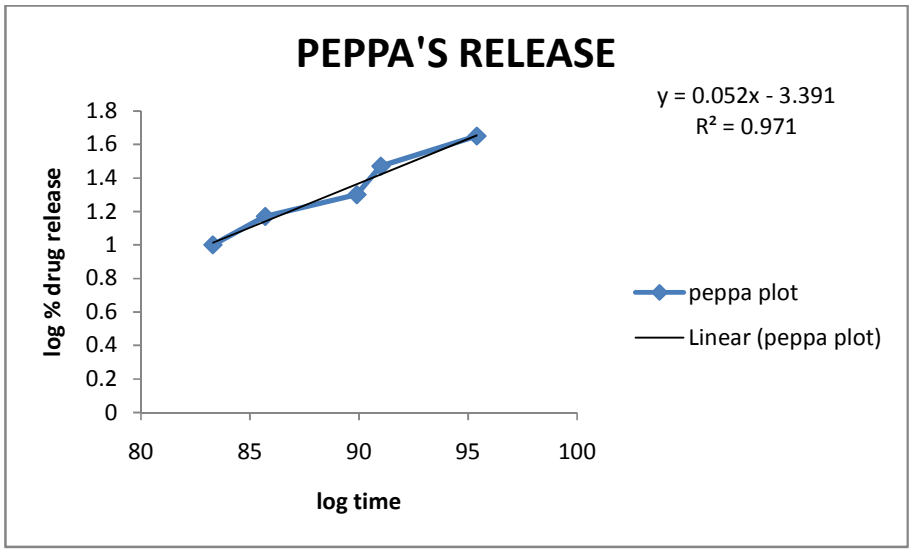
Table: 13

S.NO	Time in Mins	Square root of time	log time	% drug release	log % drug release	% drug remaining	Log % drug remaining
1	10	3.162	1	83.3	1.92	16.7	1.22
2	15	3.87	1.17	85.7	1.93	14.3	1.15
3	20	4.47	1.30	89.9	1.95	10.1	1.0
4	30	5.47	1.47	91.0	1.95	9	0.95
5	45	6.47	1.65	95.4	1.97	4.6	0.66




FIRST ORDER RELEASE
y = -0.015x + 1.366
R² = 0.968
Alog %drug remaining
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
time mins
first order plot
Linear (first order plot)

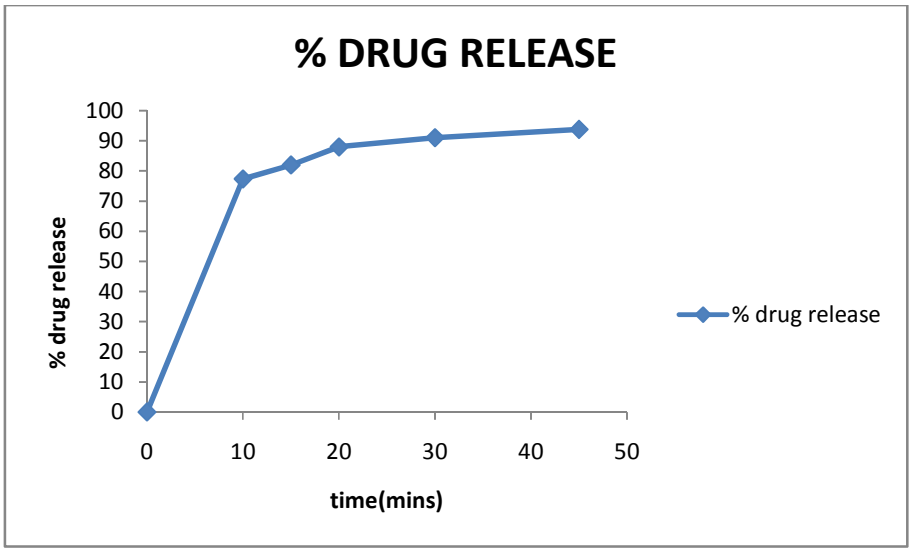

HIGUCHI RELEASE
y = 3.329x + 73.29
R² = 0.957
% drug release
98
96
94
92
90
88
86
84
82
0
2
4
6
8
square root
higuchi plot
Linear (higuchi plot)



FORMULATION 6

Table: 14

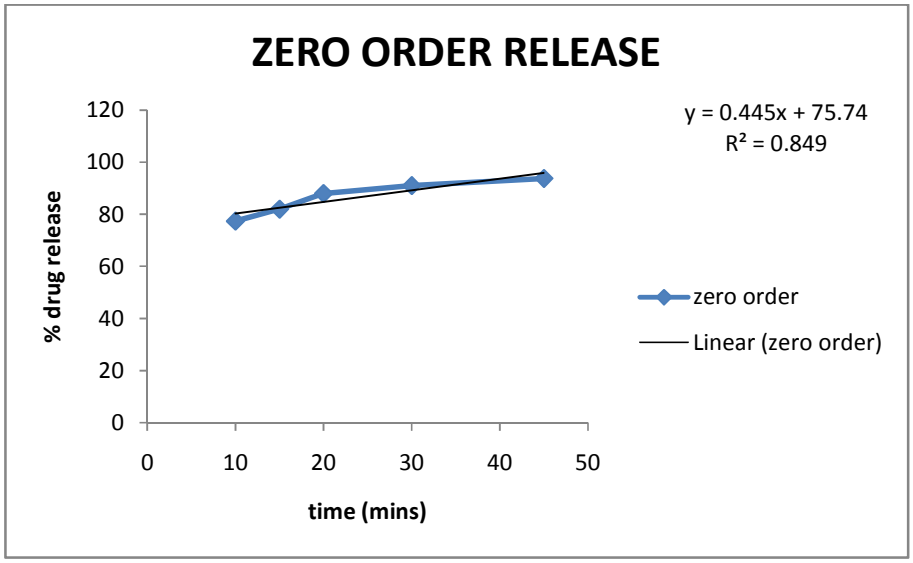
S.NO	Times in (mins)	Absorbance (nm)	concentration	Amount of drug release (mg)	Amount of drug release mg/1000	Cumulative of % drug release	% drug release
1	10	0.279	1.522	0.015	15.22	15.24	77.38
2	15	0.296	1.61	0.016	16.1	16.14	81.9
3	20	0.318	1.73	0.017	17.32	17.33	88.0
4	30	0.329	1.79	0.017	17.91	17.93	91.1
5	45	0.339	1.84	0.018	18.46	18.48	93.8

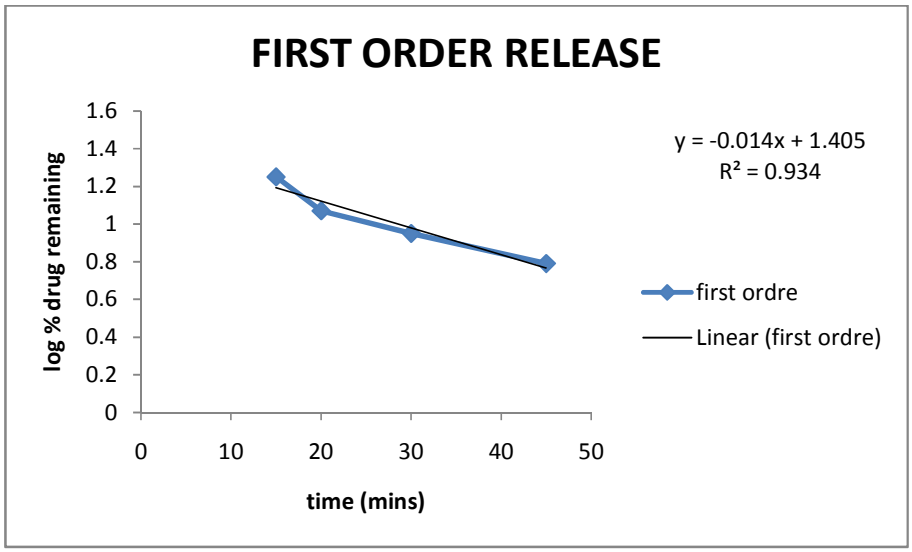


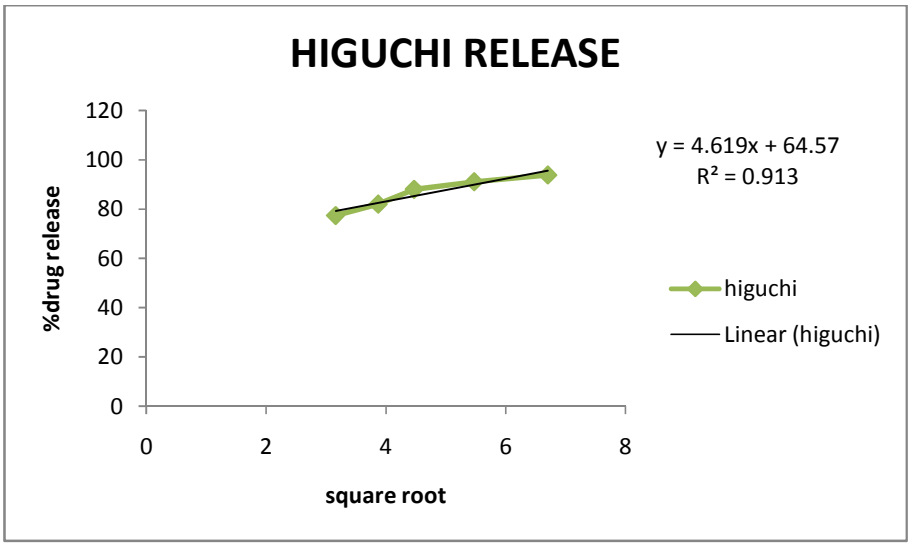
KINETICS OF DRUG RELEASE:

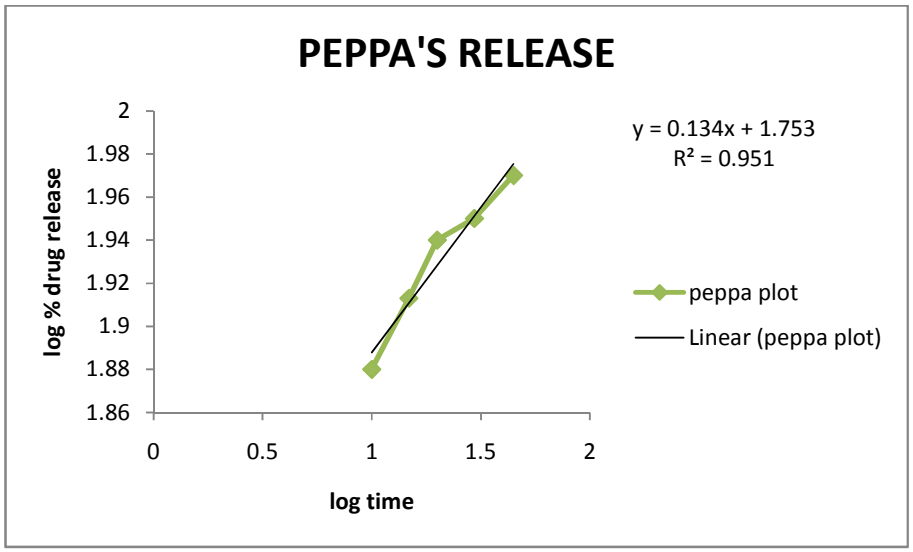
Table: 15

S.NO	Time in Mins	Square root of time	log time	% drug release	log % drug release	% drug remaining	Log % drug remaining
1	10	3.162	1	77.3	1.88	22.62	1.354
2	15	3.87	1.17	81.9	1.91	18.03	1.255
3	20	4.47	1.30	88	1.94	12	1.07
4	30	5.47	1.47	91.1	1.95	8.95	0.95
5	45	6.47	1.65	93.8	1.97	6.2	0.79




FIRST ORDER RELEASE
log % drug remaining
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
time (mins)
y = -0.014x + 1.405
R² = 0.934
first ordre
Linear (first ordre)

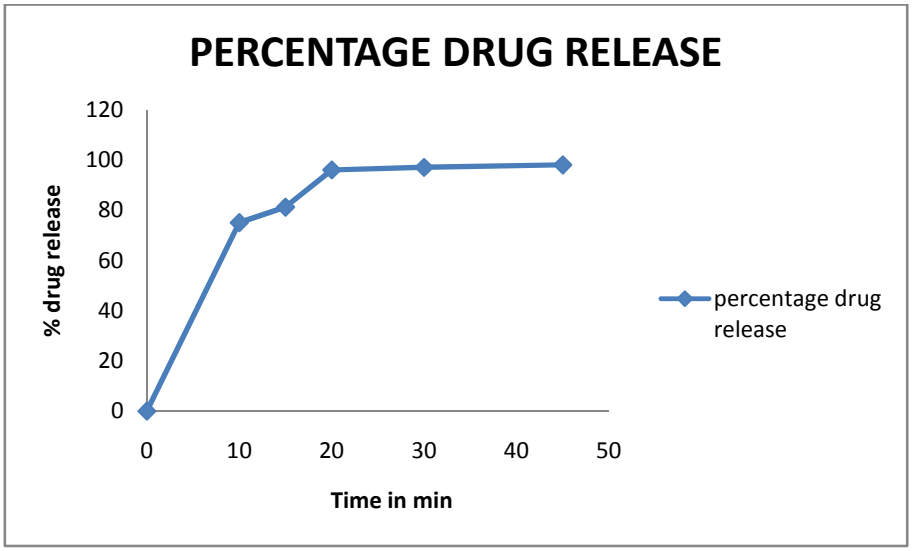

HIGUCHI RELEASE
%drug release
120
100
80
60
40
20
0
0
2
4
6
8
square root
y = 4.619x + 64.57
R² = 0.913
higuchi
Linear (higuchi)



MARKETED PRODUCT

Table: 16

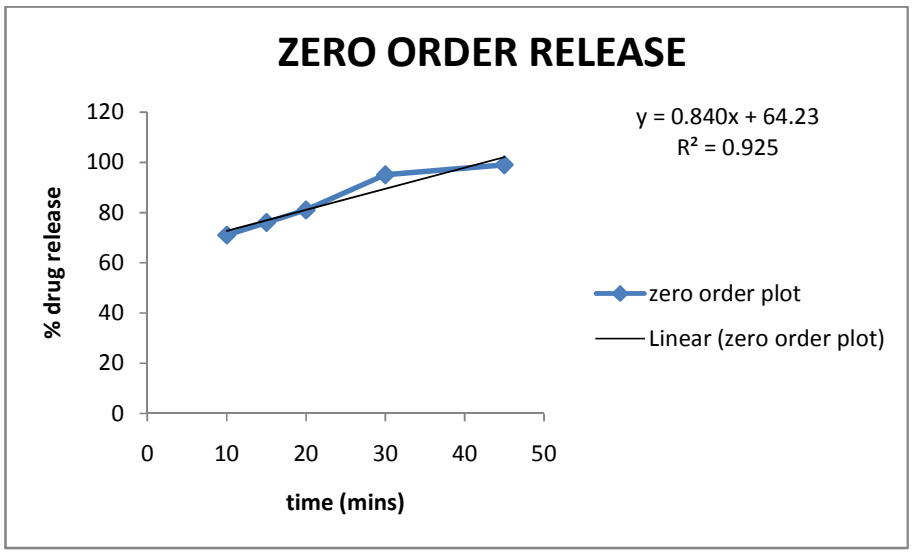
S.NO	Times in (mins)	Absorbance (nm)	concentration	Amount of drug release (mg)	Amount of drug release mg/1000	Cumulative of % drug release	% drug release
1	10	0.307	1.67	0.016	16.72	16.74	84.96
2	15	0.315	1.71	0.017	17.15	17.17	87.1
3	20	0.345	1.87	0.018	18.80	18.82	95.4
4	30	0.347	1.88	0.018	18.91	18.93	96.0
5	45	0.355	1.93	0.019	19.35	19.36	98.2+

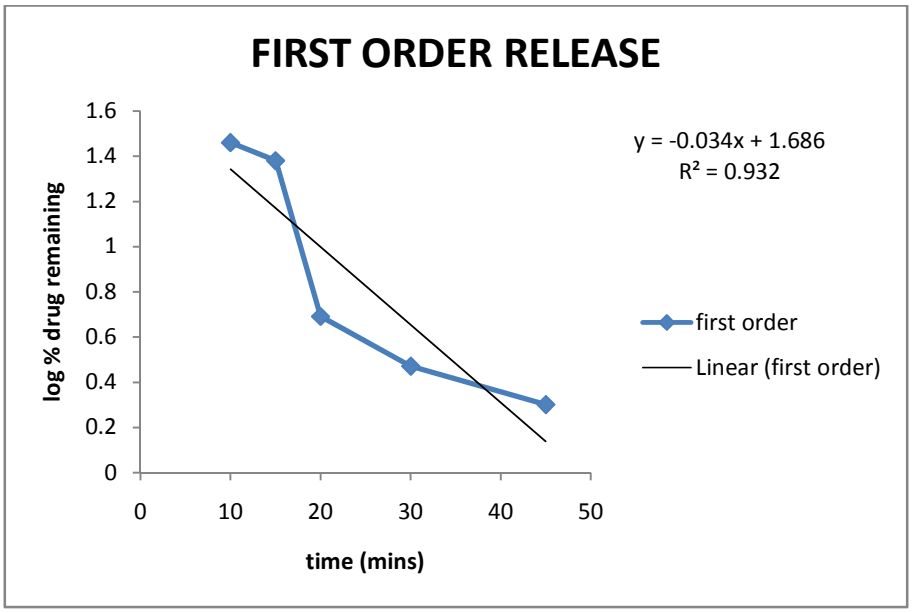


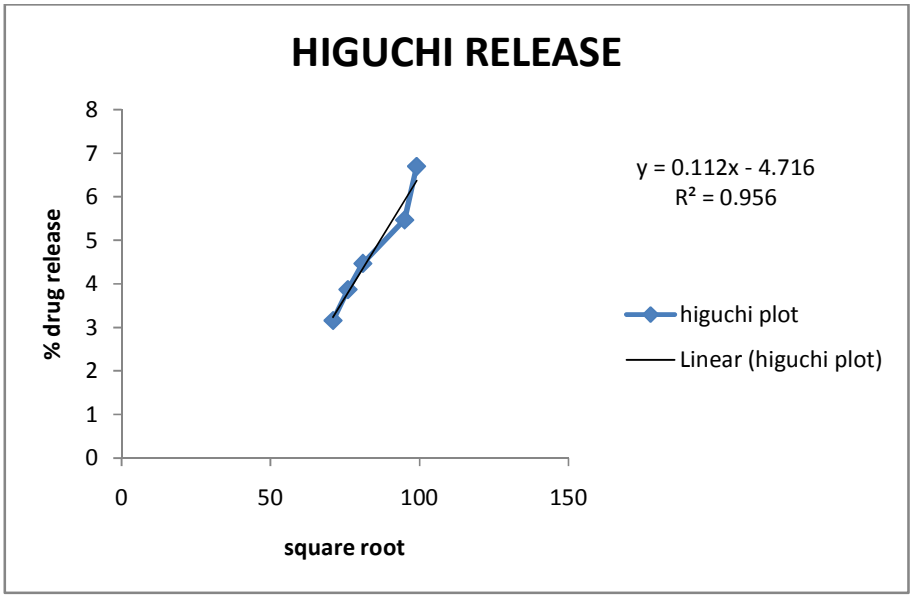
KINETICS OF DRUG RELEASE:

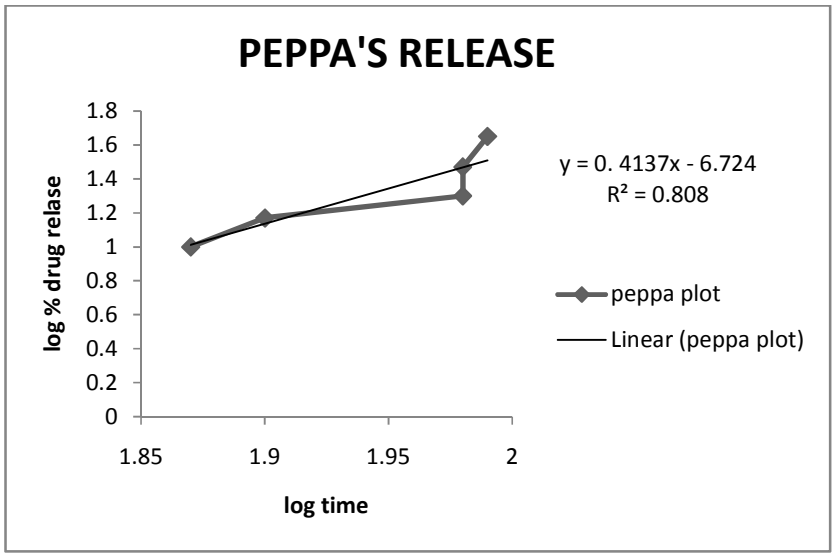
Table: 17

S.NO	Time in Mins	Square root of time	log time	% drug release	log % drug release	% drug remaining	Log % drug remaining
1	10	3.162	1	84.9	1.924	16	1.204
2	15	3.87	1.17	87.1	1.939	13	1.113
3	20	4.47	1.30	95.48	1.977	5	0.698
4	30	5.47	1.47	96.0	1.982	4	0.602
5	45	6.47	1.65	98.24	1.991	2	0.301

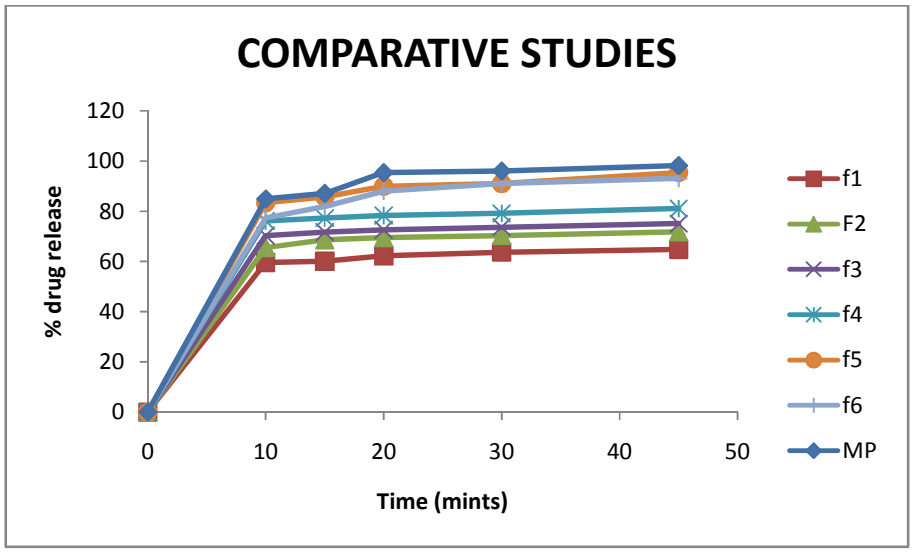



FIRST ORDER RELEASE
log % drug remaining
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
time (mins)
y = -0.034x + 1.686
R² = 0.932
first order
Linear (first order)


HIGUCHI RELEASE
% drug release
8
7
6
5
4
3
2
1
0
0
50
100
150
square root
y = 0.112x - 4.716
R² = 0.956
higuchi plot
Linear (higuchi plot)



COMPARATIVE STUDY *INVITRO* DRUG RELEASE PROFILE OF TADALAFIL ORAL JELLY



SIMILARITY FACTORS

Comparative studies with marketed Product

Table: 18

Time	F1	F2	F3	F4	F5	F6	MP
0	0	0	0	0	0	0	0
10	59.5	65.5	70.2	76.1	83.3	77.3	84.9
15	60	68.6	71.6	77.2	85.7	81.9	87.1
20	62.2	69.5	72.5	78.2	89.9	88	95.6
30	63.6	70.2	73.6	79.1	91.1	91	96
45	64.7	71.8	75	81	95.4	93	98.2
F2 value	50.64	56.72	61.80	70.93	93.58	86.30	------

Cumulative data of release of kinetics (F1 TO F6)

Table: 19

F.Code	Zero order plot	First order plot	Higuchi plot	Korsemeyer peppas plot		Possible mechanism of drug release
	R^2	R^2	R^2	R^2	n	
F1	0.947	0.949	0.984	0.926	0.067	Fickian release
F2	0..854	0.909	0.930	0.902	0.061	Fickian release
F3	0.836	0.85	0.903	0.997	0.062	Fickian release
F4	0.981	0.985	0.992	0.957	0.030	Fickian release
F5	0.927	0.968	0.957	0.971	0.052	Fickian release
F6	0.849	0.934	0.913	0.951	0.134	Fickian release
MP	0.925	0.932	0.956	0.808	0.413	Fickian release

DRUG CONTENT ESTIMATION:-

SAIMIRRA

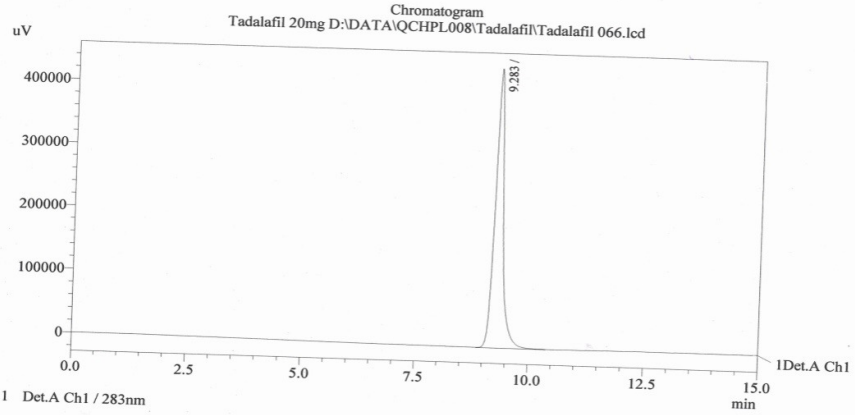
Sample Information

Mobile phase:Acetate Buffer:Acetonitrile(70:30)
Acetate buffer pH 2.8:Dissolve 4 g of anhydrous sodium acetate in about 840ml of water, add sufficient glacial acetic acid to adjust the p
Column:Phenomenex C18,250 x 4.6mm
Flow rate:1.2ml/minute
Wavelength:283nm
Load:20µl

Acquired by	: C.Prabhu
Sample Name	: Tadalafil 20mg
Sample ID	: Assay std
Tray#	: 1
Vail#	: 1
Injection Volume	: 20 uL
Data Filename	: Tadalafil 066.lcd
Method Filename	: Tadalafil.lcm
Batch Filename	: Tadalafil..lcb
Report Filename	: Report Format...lcr
Date Acquired	: 11/15/2013 4:45:33 PM

Chromatogram

Tadalafil 20mg D:\DATA\QCHPL008\Tadalafil\Tadalafil 066.lcd



1 Det.A Ch1 / 283nm

PeakTable

Detector A Ch1 283nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.283	5689762	438593	100.000	100.000
Total		5689762	438593	100.000	100.000

SAIMIRRA

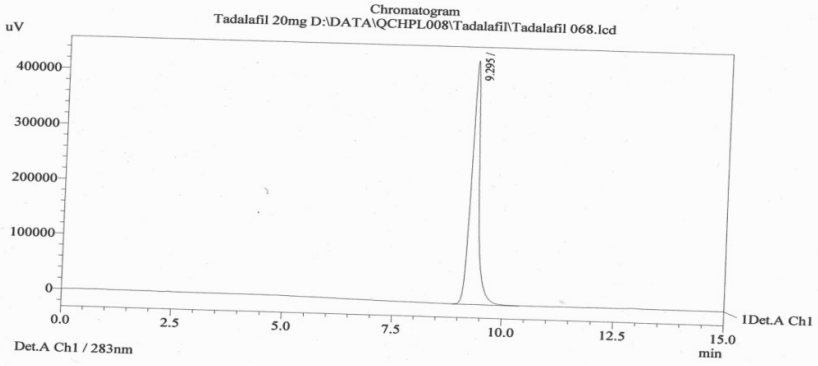
Sample Information

Mobile phase:Acetate Buffer:Acetonitrile(70:30)
Acetate buffer pH 2.8:Dissolve 4 g of anhydrous sodium acetate in about 840ml of water, add sufficient glacial acetic acid to adjust the I
Column:Phenomenex C18,250 x 4.6mm
Flow rate:1.2ml/minute
Wavelength:283nm
Load:20µl

Acquired by	: C.Prabhu
Sample Name	: Tadalafil 20mg
Sample ID	: Trial-5 (Test A1)
Tray#	: 1
Vail#	: 2
Injection Volume	: 20 uL
Data Filename	: Tadalafil 068.lcd
Method Filename	: Tadalafil.lcm
Batch Filename	: Tadalafil..lcb
Report Filename	: Report Format...lcr
Date Acquired	: 11/15/2013 5:17:08 PM

Chromatogram

Tadalafil 20mg D:\DATA\QCHPL008\Tadalafil\Tadalafil 068.lcd



1 Det.A Ch1 / 283nm

Detector A Ch1 283nm

PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.295	5710803	439371	100.000	100.000
Total		5710803	439371	100.000	100.000

SAIMIRRA

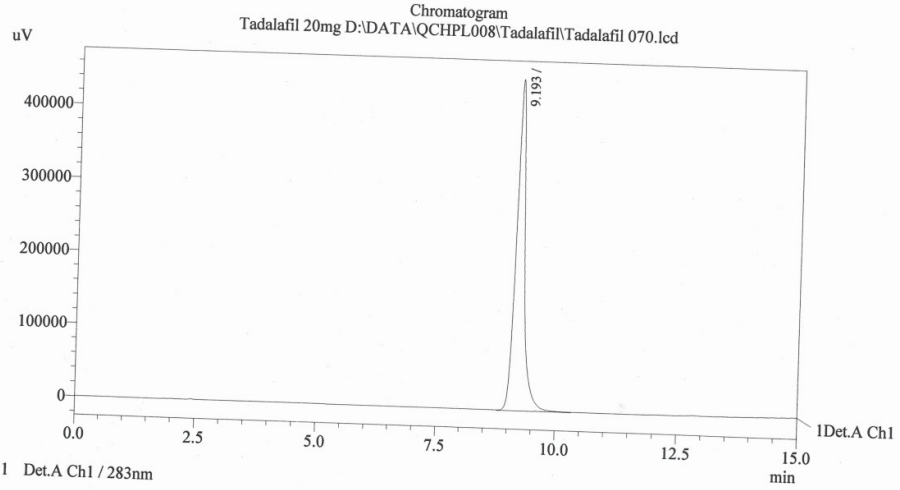
Sample Information

Mobile phase:Acetate Buffer:Acetonitrile(70:30)
Acetate buffer pH 2.8:Dissolve 4 g of anhydrous sodium acetate in about 840ml of water, add sufficient glacial acetic acid to adjust the p
Column:Phenomenex C18,250 x 4.6mm
Flow rate:1.2ml/minute
Wavelength:283nm
Load:20µl

Acquired by	: C.Prabhu
Sample Name	: Tadalafil 20mg
Sample ID	: Trial-5 (Test A2)
Tray#	: 1
Vail#	: 3
Injection Volume	: 20 uL
Data Filename	: Tadalafil 070.lcd
Method Filename	: Tadalafil.lcm
Batch Filename	: Tadalafil..lcb
Report Filename	: Report Format...lcr
Date Acquired	: 11/15/2013 5:48:38 PM

Chromatogram

Tadalafil 20mg D:\DATA\QCHPL008\Tadalafil\Tadalafil 070.lcd



1 Det.A Ch1 / 283nm

PeakTable

Detector A Ch1 283nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	9.193	5786422	451761	100.000	100.000
Total		5786422	451761	100.000	100.000

PERCENTAGE OF DRUG RELEASE

Table: 20

S. No	Formulation	% Drug Release
		TADALAFIL
1	M P	99.6
2	F1	72.34
3	F2	70.25
4	F3	70.63
5	F4	81.63
6	F5	98.8
7	F6	95.23

STABILITY STUDIES

Physical And Chemical Parameters Of Optimized Formulation F5 After 1^{st}, 2^{nd} And 3^{rd} Month At20 -25^{0}

Table: 21

Parameter	Initial	After 1^{st} month	After 2^{nd} month	After 3^{rd} month
Appearance	Transparent,opaque,milky white Semisolid jelly	No change	No change	No change
Ph	8.0	7.9	8.0	8.1
Viscosity (dyne sec/cm^2)	294520	294520	294520	294520
Temp ^{0}c	25	25	25	25
Drug content of tadalafil (%)	98	98	98	98

10. DISCUSSION

The results of the present study demonstrated that delivery of tadalafil oral jelly could be beneficial to improve the solubility as well as bioavailability of tadalafil. Tadalafil recommend in therapy of erectile dysfunction and available as tablets form. Owing to poor bioavailability of tadalafil may not control the erectile dysfunction effectively. Focusing on this in the present study an attempt was made to develop oral jelly of tadalafil using carbopol 940 with different concentration as a jelling agent. In FTIR spectra there is no disappearance of peak present in drug and physical mixture it shows the compatibility of drug and polymer.

The result of physico-chemical parameter such as pH, appearance and viscosity shown all formulation were within standard limit and compare to other F5 is considered as best in their characteristics. Invitro dissolution study results of all was formulations shows immediate release and it varied according to the concentration of carbopol 940.The percentage release of drug increased from 64.75% to 95.4% at higher concentration of polymer. The observed result complies with marketed product this f5 is considered as a best formulation.

The result of drug content estimation show &concentration of drug was higher in f5 this indicates the influence of polymer. When increasing the concentration of polymer the alteration between the polymer and drug will be increased thus increasing concentration of drug in dosage form.F2valuesof all formulation and marketed product were 50.64, 56.72, 61.80, 70.93, 93.58, 86.30 respectively and these results shows all formulations are suitable for immediate release dosage form. The observed results were fitted with release kinetics and it shows all the formulation obeys first order release with fickaian mechanism.

Stability study was performed for the best formulation and the result indicates that the prepared jelly was highly stable during its storage. Thus it was concluded among the all formulation f5 having better release characteristics due to the higher concentration of carbopol 940 and which complies with the results obtained from the marketed product and it could be beneficial to improve the bioavailability of tadalafil.

11. CONCLUSION

The present study reveals that tadalafil oral jelly released the drug as rapidly manner with improved bioavailability. The observed results were found that the concentration of carbopol 940 can influenced the release rate & other physico chemical properties. Thus it can be concluded that tadalafil jellies are beneficial in improving the bioavailability of drug as compared to other oral fast releasing dosage forms.

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