Review Article

Overture of the sildenafil citrate gels and jellies: The simplified sight

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ABSTRACT

Erectile dysfunction (ED) is high occurring disease observed with aging and in patient with several risk factors such as heart disease, hypertension, obesity, diabetes, drug related, and pelvic surgery. Endothelial dysfunction is common factor underlying pathophysiology. Sildenafil is effective in large population of patients including difficult to treat population. Sildenafil (Viagra) is used to treat ED (impotence; inability to get or keep an erection) in men. Sildenafil is used to improve the ability to exercise in adults with pulmonary arterial hypertension. The quality of life and satisfaction for treated men is well tolerated with considerable safety profile. Because sildenafil citrate is a treatment, not a cure, for ED, many men may choose to use it for an extended period. Sildenafil citrate also shows some side effects. The common side effects are headaches, feeling sick, hot flushes, indigestion, stuffy nose, etc., some of the serious side effects are chest pain. By preparing the fast-dissolving oral thin film of compositions, comprising bitter tasting sildenafil citrate and the bitter taste masking agent of sodium hydroxide, sodium bicarbonate or the mixtures there of, this invention provides a formulation of an excellent fast-dissolving oral thin film which can mask the bitter taste of sildenafil citrate and thus mitigating an unpleasant feelings at time of drug administration.

Keywords: Clinical trial, erectile dysfunction, sildenafil citrate, taste masking

Introduction

Male sexuality, a complex physiological process, is an important part of the quality of life. About 30 million people in United States are suffering from male erectile dysfunction (ED) also called as impotence which is characterize by inability to maintain and/or attain erectile state of penis for sufficient and satisfactory sexual intercourse.[1] This dysfunction can be partial decrease in rigidity to complete failure to erect. Organic and psychological aspects can be related to it.[2] Along with age, diabetes, hypertension, multiple sclerosis, and medications are some of the risk factors that can be responsible, for ED.[3,4] Dilation of penile arteries and relaxation of corporal smooth muscle in penis results in hemodynamic event of erection. The penis is lengthened by pair of tubular structure, the corpus cavernosum which is composed of thousands of tiny sacs each surrounded by smooth muscle cells. On receiving stimulation (either physical or brain) these muscles relax, allowing blood to fill small sacs while when flaccid, the tone of muscle around sacs increases, and sacs remain collapsed. The tunica is tough; inelastic membrane just beneath skin of penis encircles the cavernosa which when filled with blood expands against tunica. These veins squeezed closed, keeps sacs engorged with blood resulting in full erection. Therefore, to produce full erection a sufficient blood supply, nerve function with hormone operation is of utmost importance.[5,6]

A vital part of life essential for good health and reproduction, normal sexual function, is an intricate process affected by level of sex hormones. It is also said to be neurogenic as well as psychogenic. Male ED is a complex process involving various risk and pathogenic factors affecting directly and indirectly. Other factors contributing apart from physical and psychological are comorbities and medication used to treat diseases. Lifestyle of ageing man and behavior, androgen deficiency can often contribute to the lower testosterone level to affect sexual function.[7] Importantly, ED is no longer simply confined to sexual activities but acts as an indicator of systemic endothelial dysfunction1.[8] From a clinical standpoint, ED often precedes cardiovascular events and can be used as an early marker to identify men at high risk of major cardiovascular disease six. In this primer, we describe the different etiologies of ED and the currently available treatments.[9]

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Etiology of Male ED

Amongst different causes of ED CVS disease, diabetes, hypertension, high cholesterol, obesity, kidney disease, drug use, alcohol consumption, stress, etc., are prime causes. The disease can be caused by one or several of these factors.[10] Impaired arterial blood flow, or arterial insufficiency are most common cause of ED. Medical disorders affecting the arterial system may interfere with the corporal veno-occlusive mechanism, resulting in its failure to trap blood within the penis or producing leakage so that an erection cannot be maintained. Erectile function originates in the brain, where neural impulses travel down the spinal cord and affect the genital region.[11] It can occur at any stage of erection process. Nitric oxide (NO) and prostaglandins when released into blood stream by neuronal signals stimulate smooth muscles in cavernosa to relax, and an erection happens. These nerve impulses might be interrupted by spinal cord injury, prostate surgery, multiple sclerosis, and neuropathy associated with diabetes or alcoholism and also with hormone imbalance.[12] Testosterone concentrations ordinarily decline with age and are associated with lessened sexual interest and fewer nighttime erections. Testosterone concentrations are antagonized by prolactin. Hyperprolactinemia may be caused by treatment with any of a variety of commonly used medications (e.g., buspirone, cimetidine, estrogens, haloperidol, enalapril, methyldopa, phenytoin, and ranitidine). Testosterone and its active metabolite, dihydrotestosterone, bind to an intracellular protein receptor on the human androgen receptor.[13]

ED may be caused by diseases that interfere with libido, and therefore the brain's perception of arousal, such as Alzheimer's, stroke, Parkinson's, or brain trauma. Injury to the spinal cord may interrupt neural pathways to the sacral region, preventing or inhibiting the process of achieving an erection.[14] Hormones such as adrenocorticotropic hormone, oxytocin, prolactin, and androgens, especially testosterone, have been implicated in the modulation of erectile function. NO is thought to be the main vasoactive neurotransmitter involved in the erectile response and is released from non-adrenergic, noncholinergic (NANC) neurons as well as from the endothelium. An erection is dependent primarily on a neurovascular, NANC mechanism peripherally, and on the central nervous system.[15,16]

Testosterone-induced activation of the androgen receptor leads to an increase in erectile function. Stress and anxiety also induce impotence by raising catecholamine concentrations in the blood, which tends to oppose smooth muscle relaxation. Fear of sexually transmitted disease or pregnancy, conflict in the relationship, and performance anxiety are common psychological causes of impotence. Failure to achieve an erection increases anxiety with each subsequent attempt, perpetuating and compounding the problem.[17] Several studies have explored the epidemiology of ED by considering different settings and populations. Given that ED is regarded as a condition that is more prevalent in older men, two milestone studies have provided valuable results in this setting: The Massachusetts male aging study (MMAS) and the European male aging study (EMAS). The MMAS showed a combined prevalence of mild-to-moderate ED of 52% in men aged 40–70 years; ED was strongly related to age, health status, and emotional function.[18]

Sildenafil in Male ED

Sildenafil (Viagra) is used to treat ED (impotence; inability to get or keep an erection) in men. Sildenafil (Revatio) is used to improve the ability to exercise in adults with pulmonary arterial hypertension (PAH; high blood pressure in the vessels carrying blood to the lungs, causing shortness of breath, dizziness, and tiredness). Children should not usually take sildenafil, but in some cases, a doctor may decide that sildenafil (Revatio) is the best medication to treat a child's condition. Sildenafil is in a class of medications called phosphodiesterase (PDE) inhibitors. Sildenafil treats ED by increasing blood flow to the penis during sexual stimulation. This increased blood flow can cause an erection. Sildenafil treats PAH by relaxing the blood vessels in the lungs to allow blood to flow easily, structure of sildenafil, as shown in Figure 1.[19]

Sildenafil is an oral therapy for ED of a broad range of causes. By selectively inhibiting phosphodiesterase type 5, it allows corpus cavernosum smooth muscle to relax, potentiating erections during sexual stimulation. The blood pressure is reduced transiently by sildenafil, but more marked hypotension may occur during concurrent administration of sildenafil and organic nitrates; this combination is contraindicated.[20] Sildenafil is rapidly absorbed, with dose-proportional peak plasma concentrations within 1 h of administration. The elimination half-life is 3–5 h. Dosages usually begin at 50 mg taken when needed = 1 h before sexual activity no more than once daily. The maximum dose is 100 mg when needed once daily and lower doses (e.g., 25 mg) may be used in elderly patients and those with hepatic or renal impairment or receiving cytochrome P450 enzyme CYP3A4 inhibitors, such as ritonavir, saquinavir, ketoconazole, erythromycin, or cimetidine. More than 3000 patients with ED of organic (e.g., diabetes or spinal cord injury), psychogenic or mixed origin received sildenafil 5–100 mg or placebo in fixed- or titrated-dose trials. Sildenafil was associated with dose-related improvements in the frequency, hardness, and duration of erections and in patients' abilities to achieve and maintain erections adequate for successful sexual intercourse. In titrated-dose trials, the most commonly effective doses were 50 or 100 mg, although lower doses were effective in some patients.[21] Sildenafil was significantly more effective than placebo in ED of all tested causes. The efficacy of sildenafil was not affected by patient age (> or < or = 65 years) or by antihypertensive or antidepressant medications. The drug was effective in patients with severe ED. Efficacy was maintained in long-term (1-year) studies. Sildenafil also appears to improve the quality

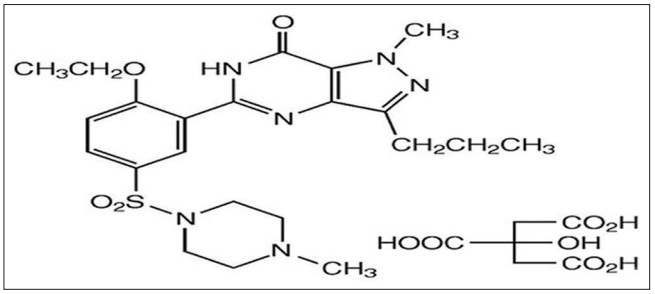

Figure 1: Sildenafil citrate structure

of life of both patients and their sexual partners. Common adverse events associated with sildenafil were transient and mild or moderate and included headache, flushing, dyspepsia, nasal congestion, and abnormal vision. Tolerability was maintained in long-term (< or = 1 year) studies. No serious sildenafil-related adverse events occurred in clinical trials; cardiovascular events seen in postmarketing surveillance generally occurred in patients with other known risk factors.[22,23]

Mechanism of Action of Sildenafil Citrate

Cyclic guanosine monophosphate (cGMP) is the second messenger for the G-protein-coupled receptors activated by endogenous substances. Intracellular concentrations of cGMP are controlled by activation of cyclic nucleotide cyclases and breakdown by phosphodiesterases (PDEs). Specifically, a number of PDE isozymes hydrolyze cGMP to the inactive guanosine monophosphate (GMP); thus concentrations may be raised by the use of a selective cGMP PDE inhibitor. There are at least seven families of PDE of which three types (PDE 1, 5, and 6) selectively hydrolyze cGMP.[24,25]

Pharmacokinetics and Metabolism of Sildenafil Citrate

In a single-masked, dose-escalation study, and single oral doses of sildenafil citrate were rapidly absorbed, with maximum observed plasma concentrations occurring within 1 h after dosing. 3° Plasma concentrations were found to decline bi-exponentially, with a mean terminal half-life of 3–5 h. The pharmacokinetics of sildenafil was found to be dose proportional over the recommended dosage range. The maximum plasma concentration (Cmax) and area under the plasma concentration curve (AUC) increased linearly as the dose increased.[26] Sildenafil is eliminated predominantly by hepatic microsomes mediated by two P450 isoforms (CYP3A4 [major] and CYP2C9 [minor]). Both sildenafil and its metabolite have terminal half-lives of about 4 h. In an open, parallel-group study investigating the absorption, metabolism, and excretion of a single oral and single intravenous dose of C14-sildenafil citrate, the absolute bioavailability and absorption of sildenafil were calculated to be 38% and 92%, respectively, indicating that the low absolute bioavailability is due to first-pass metabolism and not to incomplete oral absorption. There was no recovery of unchanged drug in urine or feces, demonstrating that the major clearance mechanism for sildenafil is metabolic. The major urinary metabolite is the aliphatic hydroxylated metabolite, accounting for 41% of the urinary radioactivity. The principal routes of metabolism of sildenafil are N-demethylation at the N-methyl pyrazole moieties, multiple oxidation, loss of a 2-carbon fragment from the piperazine ring, and aliphatic hydroxylation. Maximum observed plasma concentrations of sildenafil are reached 30–120 min (median, 60 min) after oral dosing in the fasting state. Sildenafil and its major metabolite are both approximately 96% bound to plasma proteins. For the major metabolite, the maximum observed concentrations occurred within 1 h of dosing.[27,28]

The elimination half-life for this metabolite is of the same order as that of the parent drug, between 3 and 4 h. A pharmacokinetic study in healthy elderly (>65 years of age) and young volunteers demonstrated that the AUC and Cmax of sildenafil and its metabolite were almost doubled in the elderly subjects. This difference in plasma concentrations could be partially attributable to differences in oral clearance. The fraction of unbound drug was smaller in the elderly compared with the young subjects, and this difference in protein binding might result in differences in volume of distribution, leading to the elevated plasma concentrations seen in elderly subjects. The relationship between AUC and age for sildenafil and its metabolite was not attributable to age-related differences in creatinine clearance. Inclusion of age and creatinine clearance in the regression model showed that the effect of age was statistically significant ($P = 0.0055$), whereas the effect of creatinine clearance was not known earlier.[28,29] Sildenafil is an effective oral treatment in men with ED. It was significantly superior to placebo in improving erections and allowing successful penetrative sexual intercourse. Although its place in disease management is still emerging and there are contraindications to its use, if preliminary positive reports are confirmed, sildenafil will be the pre-eminent first-line therapy for ED.[30]

Adverse Events of Sildenafil Citrate

Like any other medicine sildenafil citrate also shows some side effects. The common side effects are headaches, feeling sick, hot flushes, indigestion, stuffy nose, etc., some of the serious side effects are chest pain (during and after sex), prolonged painful erections, a sudden increase, or decrease in vision. Sometimes serious skin reactions with fever, severe peeling and swelling of skin, mouth blistering, swelling around genitals, and eye can be observed. Seizures may precipitate sometimes. In rare cases anaphylaxis may observed.[31]

Clinical Trials of Sildenafil

In one of the early clinical study of sildenafil, patients reported headache, backache, dyspepsia, and pelvic musculoskeletal pain after doses of 25 and 50 mg. With the exception of one patient reporting severe headache, these adverse effects were mild and transient. There were no significant changes in heart rate, blood pressure, or laboratory test results. In a 28-day study, sildenafil was well tolerated.[32] Mild and transient headache, dyspepsia, and muscle aches were the most frequently reported side effects. In a larger 28-day study enrolling 351 men with ED, treatment was generally well tolerated; headache, flushing, and dyspepsia were noted more often in the sildenafil group than in the placebo group. The overall number of patients discontinuing therapy because of adverse events was <5% of the original 351 patients, with similar proportions of discontinuation in all treatment groups. In the dose-response and dose-escalation studies, sildenafil treatment was well tolerated. The main adverse effects were headache, flushing, dyspepsia, rhinitis, and visual disturbances, most of which were mild. One man with a visual disturbance discontinued treatment; he had also experienced flushing. One man stopped taking sildenafil because of treatment-related headache and flushing.[33]

Laboratory findings on blood chemistry and hematology tests indicated no abnormalities. Transient visual disturbances (changes in

perception of color hue or brightness) were reported in 18 of 316 sildenafil-treated patients in the dose-response study, 4 of 163 in the dose-escalation study, and 9 of 225 in the open-label dose-extension study. The frequency of these adverse effects increased with increasing doses of sildenafil, although the symptoms were usually mild and lasted for only few minutes to a few hours after dosing. No patient reported priapism during any of the studies. In the 32-week, open-label, sildenafil study, 4 of 207 men (1.9%) withdrew because of treatment-related adverse effects (headache in two, intermittent flushing and blurred vision in one, and groin pain and headache in one).[33,34]

The adverse effects most commonly reported in these studies result from sildenafil's pharmacologic nature as a PDE5 inhibitor (headache, flushing, and dyspepsia) and a weak PDE6 inhibitor (visual effects). The drug has modest vasodilatory properties but no effect on heart rat. Adverse events that were reported in >2% of patients treated with sildenafil and were reported more frequently in the treatment group than in the placebo group in flexible-dose Phases II and III studies are listed in the table.[34] In another early human trials in 1991 and 1992 established that sildenafil was not promising as an antinational drug; however, as an "adverse event" in the trials, men were reporting an erectogenic effect from the medication. In 1992, at the University of California, Los Angeles, the link between NO and erections was established.[35] Dr. Jacob Rajfer and his collaborators clearly showed the link between NO and penile smooth muscle relaxation during penile erection 1–3. In late 1993, the first study of sildenafil for the treatment of ED was so successful that men and their partners protested when the trials were completed and the medication withdrawn; open-label extensions were added to the placebo-controlled studies.[36] By the time, the manufacturer was ready to submit to the U.S. Food and Drug Administration (FDA) on September 29, 1997, over 4500 men had been tested – far more than the average number tested in the course of a typical drug development. Because this medication "fulfilled a significant medical need or represented a significant medical advance in therapy," the FDA notified the manufacturer that it would give sildenafil citrate a priority review. Approval was anticipated within 6 months instead of the usual 12 months.[36,37]

Postmarketing Data

The only contraindication to sildenafil use arises from its ability to inhibit cGMP specific PDE5. Since the drug potentiates the hypotensive effects of nitrates, it is contraindicated in patients who are using concurrent nitrates in any form. Several double-masked, placebo-controlled, interaction studies in patients using sublingual nitroglycerin, the nitroglycerin patch, or isosorbide mononitrate have shown sudden large drops in systemic blood pressure when these patients used concomitant sildenafil. For example, a patient with unstable angina might take sildenafil and begin to engage in sexual activity, the aerobic effort of which might precipitate an anginal attack. If the patient were then to take a sublingual nitroglycerin tablet while the sildenafil was still active, he could become acutely and dangerously hypotensive.[38] Such an effect could lead to dizziness or light-headedness, syncope, and a significant lowering of coronary perfusion and conversion of an area of myocardial ischemia to infarction, ultimately resulting in death. The use of isosorbide mononitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, isosorbide dinitrate/phenobarbital, and illicit substances containing organic nitrates (amyl nitrate or nitrite, butyl nitrate) should be avoided when using sildenafil adverse events, as shown in Table 1.[38,39]

Mild and transient, predominantly color disturbances, but also increased sensitivity to light or blurred vision. The potentiating effect of sildenafil to the lower blood pressure in patients using nitrate therapy has not been observed with other vasodilators. Safety data from a clinical pharmacology study in patients taking drug suggest that patients who take antihypertensive medication are not at higher risk for developing adverse symptoms associated with the lowering of blood pressure.[39] This applies to patients with stable angina taking sublingual glyceryl trinitrate, 4° oral isosorbide mononitrate, 4° calcium channel blockers, or warfarin. Under the Freedom of Information Act, the FDA has made public reports submitted to them and to Pfizer regarding fatalities in men who engaged in sexual activity after taking sildenafil. Although there have been approximately 100 reports of serious adverse reactions and 130 reported deaths in men taking sildenafil, the FDA has not asked for the drug to be removed from the market.[40] In reviewing these reports, it is necessary to understand the limitations associated with data derived from spontaneous reports. In some cases, the reported clinical data were incomplete, making it impossible to determine whether the drugs in question caused the reported reactions.

Furthermore, a given reaction may be due to an underlying disease process or another coincidental factor. Most of the men who died were elderly and had additional health problems. These case reports, which are also in Pfizer's files, will become part of their New Drug Application. The FDA reviews adverse effect profiles closely in conjunction with the pharmaceutical manufacturers. Following are examples of fatalities that occurred in individuals of various ages who were taking sildenafil in conjunction with other medications and who had a history of specific disease states.[40,41] These cases were randomly chosen from the available cases; additional case reports can be found on the US FDA Web site. A 63-year-old man taking glipizide, allopurinol, and aspirin therapy had a history of type II diabetes mellitus, hypercholesterolemia, hypertension, and paroxysmal atrial

Table 1: Adverse events reported in > 2% of patients treated with Sildenafil and reported more frequently in the treatment group than in the placebo group*

Adverse event	% of patients reporting event	
	Sildenafil (n=734)	Placebo (n=725)
Headache	16	4
Flushing	10	1
Dyspepsia	7	2
Nasal congestion	4	2
UIT	3	2
Abnormal vision	3	0
Diarrhea	3	1
Dizziness	2	1
Rash	2	1

*Obtained from package insert for sildenafil citrate

fibrillation. About 1 h after taking sildenafil and engaging in sexual activity, he had a hemorrhagic stroke and died in the hospital.

A 64-year-old man receiving isosorbide mononitrate therapy had a history of cardiomyopathy, coronary artery disease, adult-onset diabetes mellitus, and possible angina. He took one dose of sildenafil, engaged in sexual activity, and fainted. Attempts to resuscitate him were unsuccessful; the cause of death was listed as ventricular arrhythmia and myocardial ischemia.[41]

A 60-year-old man whose medical history and concomitant medications were unknown died 1 day after receiving a prescription for sildenafil. It is not known whether the patient took the medication; the cause of death was not listed.

A 73-year-old man receiving that terazosin therapy had a history of hypertension. After his second dose of sildenafil, the patient collapsed during sexual activity. At the hospital he was found to have experienced a brain-stem stroke and myocardial infarction. He died without regaining consciousness. The cause of death was not listed.[41]

A 48-year-old man, whose use of concomitant therapy was not known, had a history of diabetes. After taking sildenafil, the patient had chest pains during sexual activity. He was given nitroglycerin in the ambulance. The chest pain subsided and the patient were stable for 30 min. The chest pain began again and cardiac arrest occurred. The patient died in the emergency room; the cause of death was not listed.

An 80-year-old man receiving terazosin therapy had a history of chronic atrial fibrillation and benign prostatic hypertrophy. After taking sildenafil, he collapsed suddenly during sexual activity. Cause of death was not listed.[42]

A 57-year-old man, whose concomitant drugs and medical history were unknown took a dose of sildenafil and engaged in sexual activity. Immediately thereafter, he experienced severe chest pain. He was given nitroglycerin and subsequently died in the emergency room. The cause of death was not listed.

A 67-year-old man who was taking captopril, pravastatin, atenolol, and aspirin had a history of cardiac disease, hypertension, and hypercholesterolemia. Approximately 1 h after taking sildenafil and engaging in sexual activity, the patient's skin appeared gray and he had difficulty breathing. He was dead on arrival at the hospital, and the cause of death was not listed.[41,42]

NO is a neurotransmitter that is distributed and released in vascular smooth muscle and that causes vasodilation. Sources of NO within the cardiovascular system include the endothelium and the perivascular nerve endings. Under physiologic conditions, changes in stress on the blood vessel walls cause the release of NO, mainly from the endothelium. Circulating concentrations of NO are low and the NO molecule is labile. NO acts locally at the site of release and modulates systemic vascular resistance, thereby contributing to the control of blood pressure.[42]The effects of sildenafil on blood pressure are mild–to-moderate and are not dose-related under physiologic conditions. When patients take nitrate therapy, high concentrations of NO are present in the circulation. By inhibiting cGMP PDE5, which is present in vascular smooth muscle cells, sildenafil potentiates the vasodilatory effect of circulating NO, resulting in significant decreases in blood pressure. Sildenafil produces peripheral vasodilation, synergistically enhancing the peripheral vasodilation caused by nitrate therapy. In another study of the acute hemodynamics of intravenously administered sildenafil in patients with chronic ischemic heart disease, a blood pressure reduction from baseline of 12/11 mmHg was noted, along with a 10% increase in heart rate. A study of sildenafil (25 mg 3 times daily) taken concomitantly with glyceryl trinitrate showed that the absolute blood pressure decrease attributable to sildenafil after subtracting the pressure at baseline and with placebo was −15/−5 mmHg, with little effect on heart rate.[42]

Taste Masked Formulations of Sildenafil

Bitter taste masked oral thin film formulations of sildenafil citrate that rapidly dissolve in the oral cavity, are disclosed. By preparing the fast-dissolving oral thin film of compositions, comprising bitter tasting sildenafil citrate and the bitter taste masking agent of sodium hydroxide, sodium bicarbonate or the mixtures there of, this invention provides a formulation of an excellent fast-dissolving oral thin film which can mask the bitter taste of sildenafil citrate and thus mitigating an unpleasant feelings at time of drug administration.

Some studies have shown that Sasikumar *et al*.[47] have successfully formulated the chewable tablets of taste masked sildenafil citrate by direct compression method and wet granulation method. A12 batches using various additives were prepared and evaluated with an aim of presenting sildenafil citrate taste masked by the chewable tablet. Drug excipient compatibility study was performed by FTIR. The unpleasant taste of the sildenafil citrate was masked by intra-granular addition of dried calcium carbonate, calcium carbonate from oyster shell, and the extra-granular addition of sweeteners and flavoring agents. Taste masking study was done using alkalizing agent in different ratio. Sildenafil citrate taste masking was increased when dried calcium carbonate quantity was increased because of reduction of the solubility of sildenafil citrate. Oyster shell calcium carbonate when added to the drug did not mask the taste due to the gritty nature of it. F5 batch showed less bitterness, low disintegration time, and fast dissolution time and, hence, was taken further comparing with the innovator drug. In the present study, disintegrating properties of *Moringa oleifera* gum powder had been studied in comparison with other commercially available superdisintegrants. The isolated natural disintegrant exhibits faster drug dissolution and disintegration. The isolated gum powder can be effectively used as disintegrant for sildenafil citrate with the added advantage of the folkloric aphrodisiac activity of it. The physicochemical evaluation results for the powdered blend of all trials pass the official limits in the angle of repose, compressibility index, Bulk density, Tapped density, and Hausner's ratio.

Conclusion

ED in men can be effectively controlled using sildenafil citrate as it is found to be superior in improving erection with successful penetration during intercourse. A good safety and tolerability profile were established in men with ED. It is also effective in several

subpopulations although efficacy is lower in the so-called difficult-to-treat subpopulations such as patients with diabetes mellitus or after radical prostatectomy, including men in older age groups. Although its place in disease management is still emerging and there are contraindications to its use, if preliminary positive reports are confirmed, sildenafil will be the pre-eminent first-line therapy for ED. The quality of life of both patient and partner can be improved.

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