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Formulation and Evaluation of Sildenafil Citrate Nanosuspension

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ABSTRACT

In the present study, an attempt was made to prepare oral Nanosuspension of Sildenafil citrate is a vasoactive agent used to treat erectile dysfunction and reduce symptoms in patients with pulmonary arterial hypertension. Nano suspension containing the drug were prepared by precipitation method using combinations of polymers (such as PVP K-25, Sodium lauryl sulphate (SLS), TWEEN-80, poloxamer (188), and methanol). Estimation of Sildenafil citrate was carried out spectrophotometrically at 293nm. The Oral Nanosuspension were evaluated for various physical and biological parameters, drug content uniformity, particle size analysis, zeta potential, in-vitro drug release, short-term stability, drug- excipient interactions (FTIR). IR spectroscopic studies indicated that there are no drug-excipient interactions. The formulations F1 to F9 (containing PVP K-25, TWEEN-80, SLS, Poloxamer (188), and Methanol) used different ratio were found to be promising, of that formulation F3 containing PVP-K25 showed 99.85% release at the end of 20min & it follows zero order drug release kinetics. These formulations have displayed good Nanosuspension strength.

Keywords: Sildenafil citrate, oral Nanosuspension, PVP K-25, SLS, poloxamer (188), TWEEN-80, and Methanol.

INTRODUCTION

Schizophrenia is a mental disorder often Poor solubility of drug substance has always been a challenging problem faced by pharmaceutical scientists and it is increased now because more than 40% of new chemical entities are poorly water soluble. One of the most persistent problems faced by drugs with poor aqueous solubility is that their oral delivery is frequently associated with implication of low bioavailability and lack of dose proportionality. There are number of technologies like solid dispersion1-2, complexation, co-solvency, use of surfactants, etc., but they lack universal applicability to all drugs. A novel technology that can used to overcome problems associated with this method is nanosuspension, which is based on size reduction mechanism.

In the present research work an attempt was made to improve the solubility and dissolution rate of model drug Sildinafil citrate. Sildenfail is a vasoactive agent used to treat erectile dysfunction and reduce symptoms in patients with pulmonary arterial hypertension (PAH). This compound belongs to the class of organic compounds known as benzenesulfonamides. These are organic compounds containing a sulfonamide group that is S-linked to a benzene ring. Sildenafil elevates levels of the second messenger, cGMP, by inhibiting its breakdown via phosphodiesterase type 5 (PDE5). PDE5 is found in particularly high concentrations in the corpus cavernosum, erectile tissue of the penis. It is also found in the retina and vascular endothelium. Increased cGMP results in vasodilation which facilitates generation and maintenance of an erection. The vasodilatory effects of sildenafil also help reduce symptoms of PAH. Nanosuspension of sildinafil citrate is prepared by precipitation method using poloxamer 188 and PVP K25 as carriers and sodium lauryl sulphate and Tween 80 as surfactants.

MATERIAL AND METHODS

Sildenafil Citrate obtained as a gift sample from Pfizer , Sodium layuryl sulphate, polyvinyl pyrrolidine K25, poloxamer 188 and all other chemicals and solvents used are from SD Fine Chemicals, Mumbai.

Preparation of sildenafil citrate Nanosuspension by nanoprecipitation: Nanosuspension were prepared by the precipitation technique. Sildenafil citrate was dissolved in a methanol at room temperature (organic phase). This was poured into water containing different combinations of poloxamer 188 and PVP-K25 maintained at room temperature and subsequently stirred on magnetic stirrer which is stirred at rpm 2000-3000 for 15 min to allow the volatile solvent to evaporate. Addition of organic solvents by means of a syringe positioned with the needle directly into stabilizer/surfactant containing water. Organic solvents were left to evaporate off under a slow magnetic stirring of the nanosuspension at room temperature for 1 hour followed by sonication for 1 hour.

Evaluation parameters of Nanosuspension Sildenafil citrate:

Drug content uniformity

10 ml of each formulation was taken and dissolved in 10 ml isotonic solution and kept overnight. 10 mg (similar as in formulation) of drug was taken and dilution was made to 10 µg/ml. The dilutions were filtered and analyzed using UV for their content uniformity. The absorbance of the formulations were read using one cm cell in a UV-Vis spectrophotometer. The instrument was set at 293 nm. The drug content in each formulation was calculated based on the absorbance values of known standard solutions.

Entrapment efficacy: The freshly prepared nanosuspension was centrifuged at 20,000 rpm for 20 min at 5°C temperature using cool ultracentrifuge. The amount of unincorporated drug was measured by taking the absorbance of the appropriately diluted 25 ml of supernatant solution at 293 nm using UV spectrophotometer against blank/control nanosuspensions. DEE was calculated by subtracting the amount of free drug in the supernatant from the initial amount of drug taken. The experiment was performed in triplicate for each batch and the average was calculated.

The entrapment efficiency (EE %) could be achieved by the following equation:

%Entrapment efficiency= Drug content *100/Drug added in each formulation

pH measurement

The pH values were measured at 25 ◦C using a pH digital meter at 20 ± 1 ◦C. The formulation was brought in contact with the electrode of pH meter and equilibrated for 1 min. This method was done in triplicate and mean was calculated along with standard deviation.

Zeta potential

There are three ways by which a solid particle (colloid) dispersed in a liquid media can acquire a surface charge. First, by the adsorption of ions present in the solution. Second, by the ionization of functional groups on the particle's surface. Third, due to the difference in dielectric constant between the particle and the medium. The zeta Potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. The potential gradually decreases as the distance from the surface increases. The most widely-used theory for calculating zeta potential was developed by Smoluchowski in 1903. The theory is based on electrophoresis and can be expressed as: $\mu = \zeta\varepsilon/\eta$

where (μ) is the electrophoretic mobility, (ε) is the electric permittivity of the liquid, (η) is the viscosity and (ζ) us the zeta potential.

Particle size and shape

Average particle size and shape of the formulated nanosuspensions was determined by using Malvern Zetasizer ZS using water as dispersions medium. The sample was scanned 100 times for determination of particle size.

***In vitro* drug release study:** in –vitro dissolution studies were performed in USP apparatus-II (LAB INDIA DS 8000), employing paddle stirrer at rotation speed of 50 rpm and 200 ml of pH 6.8 phosphate buffer as dissolution medium. Accurately weighed bulk drug and nanosuspensions were dispersed in dissolution medium. The release study is performed at 37 ± 0.5°C. Samples of 5 ml are withdrawn at predetermined time intervals and replaced with fresh medium to maintain sink condition. The samples were filtered through 0.22 µm membrane filter disc (Millipore Corporation) and analyzed for Sildenafil citrate after appropriate dilution by measuring the absorbance at 293 nm.

RESULTS AND DISCUSSION

Sildenafil citrate is a BCS class-II drug having low solubility and high permeability. Thus, it is

challenging to enhance the solubility of Sildenafil citrate particles in an aqueous solution. Solvent evaporation with precipitation has been employed to produce nanosuspension of Sildenafil citrate . The different formulative variables (1) amount of Poloxamer 188 or PVP K25 (2) amount of Tween 80 or sodium lauryl sulphate and organic to aqueous solvent ratio were contributed much towards the change in particle size in nanosuspension preparation. Determination of Sildenafil citrate λ-max was done in ph 6.8 phosphate buffer buffer medium for accurate quantitative assessment of drug dissolution rate. The λ-max was found to be 293 nm, i.e., at its absorption maxima. Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The drug content of the formulated Nanosuspension was found in the range of 85.12 to 94.29 % respectively. The entrapment efficacy of the formulated Nanosuspension was found to be in the range of respectively.

The measurement of Zeta potential itself is a particle electrophoresis, the particle velocity is determined via the doppler shift of the laser light scattered by the moving particles. The field strength applied was 20 V/cm. The electrophoretic mobility was converted to the zeta potential in mV using the Helmholtz-Smoluchowski equation. At standard measuring conditions (room temperature of 25 °C, water) this equation can be simplified to the multiplication of the measured electrophoretic mobility (μm/cm per V/cm) by a factor of 12.5, yielding the ZP in mV. The optimized batch (F3) had an average particle size of 38.1 nm. The in vitro drug release studies were compared for F1 to F9 formulations. poloxamor 188, PVP K25 used as carriers and tween 80, sodium lauryl sulphte used as surfactants in these formulations. When compared to the SLS and tween 80, the PVP K25 and poloxamer 188 drug release was more 99.81% drug was released within 15 minutes. On comparing the best optimized formula i.e., F3 with conventional formulation, it was clearly observed that the %drug release was more i.e 99.81% within 15 mins by best formulation, whereas it is 95.88% for the conventional formulation. So, the % of drug release was more in F3 Nanosuspension than the conventional tablet.

CONCLUSION

Oral Nanosuspension of Sildenafil citrate can be prepared by precipitation method using polyvinyl PVP K25, Tween 80, Sodium lauryl sulphate, Poloxamer 188 and methanol. As the amount of polymer increases, the drug release rate increases, whereas Nanosuspension strength increases. The optimized batch (F3) had a Zeta Potential and average particle size with in the acceptable range. IR spectroscopic studies indicated that there are no drug-excipient interactions. The formulations F1 to f3 (containing polyvinyl PVP K25, Poloxamer 188, methanol and water) and F4 to F6 (containing Sodium lauryl sulphate, Poloxamer 188, methanol and water) and F7 to F9(containing Poloxamer 188, Tween 80, methanol and water) were found to be promising, which showed formulation F3 is 99.85 of drug released respectively within 55 min. The formulation F3 is compared to other formulations the F3 is the best formulation of the released the percentage drug of Nanosuspension. Remaining formulation are drug releasing percentage showing respectively of Nanosuspension of Sildenafil citrate.

Table-1 : Composition of Nanosuspension of Sildenafil citrate

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Sildenafil citrate	10	10	10	10	10	10	10	10	10
PVP-K25	2.5	5	7.5						
SLS				2.5	5	7.5			
TWEEN-80							2.5	5	7.5
Poloxamer 188	1	1	1	1	1	1	1	1	1
Methanol	2	2	2	2	2	2	2	2	2
Water	40	40	40	40	40	40	40	40	40

Table-2 : *In-vitro* drug release data of formulation F1to F9

TIME (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	28.44	36.52	42.37	13.32	18.47	21.26	11.59	14.25	19.84
10	38.29	48.36	73.78	27.74	35.40	38.33	20.47	25.13	31.47
15	47.77	79.74	99.85	36.52	47.23	49.27	34.28	39.85	44.59
20	74.15	85.11		55.79	59.85	68.84	47.75	51.28	57.91
25	88.02	97.85	-	65.22	75.77	83.69	58.97	62.26	73.14
30	99.16	-	-	79.02	88.64	99.04	69.07	74.83	89.78
35				84.39	98.61	-	77.88	80.13	98.22
40				96.11	-	-	85.54	88.47	
45							93.83	96.76	

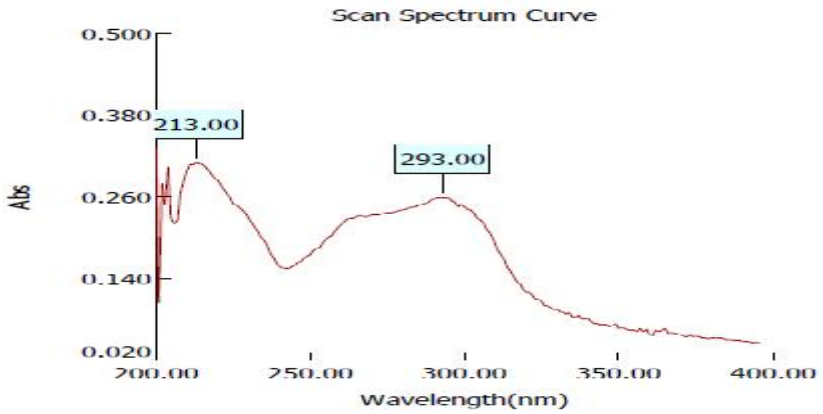

Figure-1 : uv spectrum of Sildenafil citrate293 nm

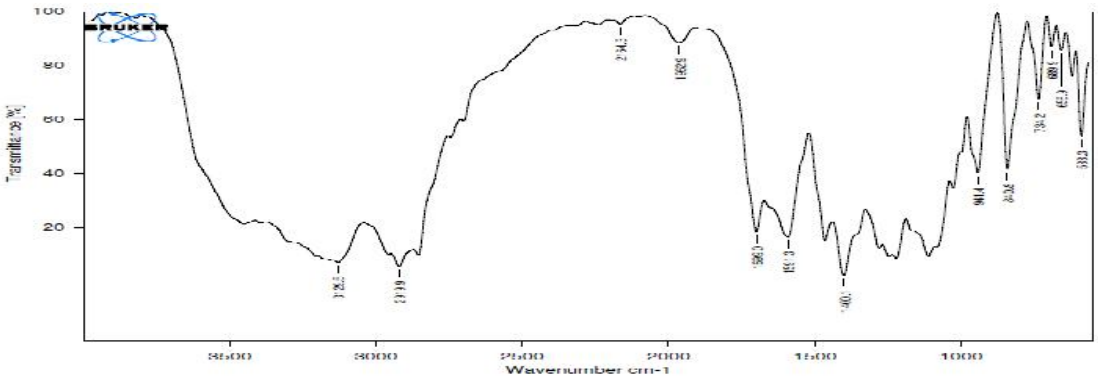

Figure-2: IR spectrum of Sildenafil citrate Optimised Formulation

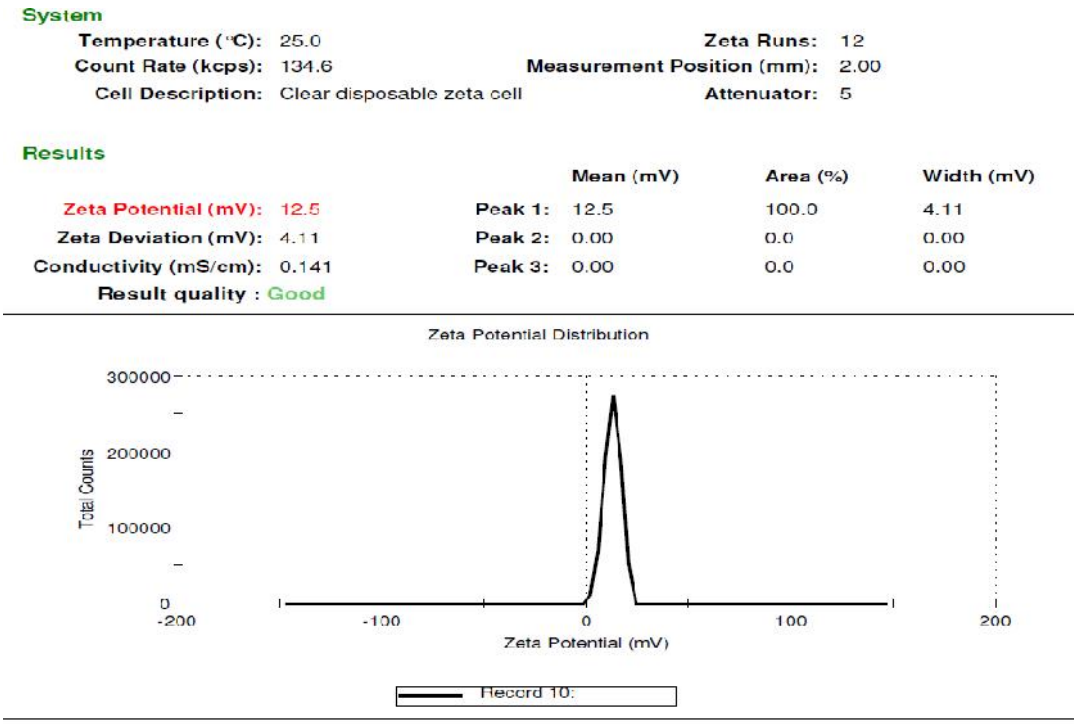

Figure-3 : Zeta Potential Analysis

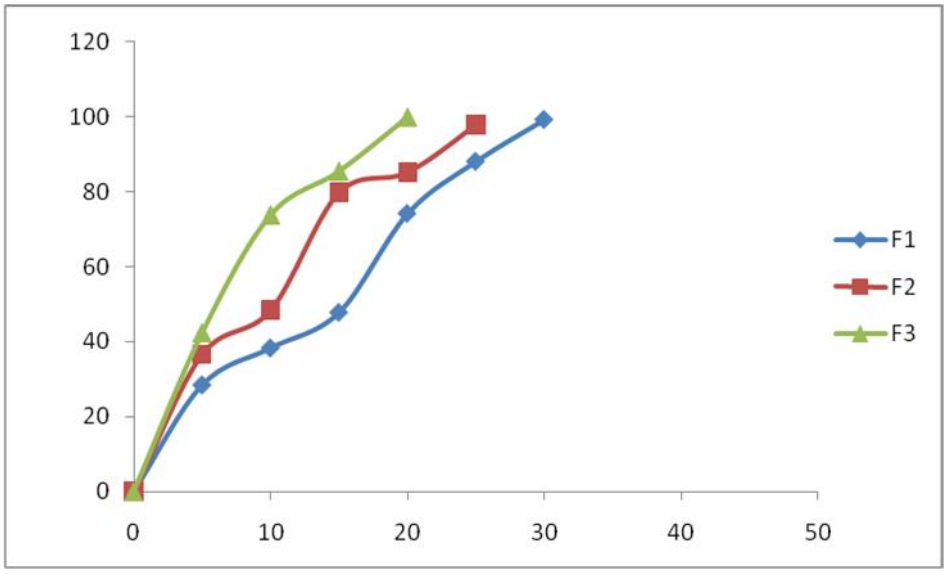

Figure-4: Dissolution parameters for the formulations F1, F2, F3

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