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Influence of natural, synthetic polymers and fillers on sustained release matrix tablets of sildenafil citrate

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ABSTRACT

The purpose of the present investigation was to design and evaluate influence of natural, synthetic polymers and fillers on sustained release matrix tablets of sildenafil citrate and to select the best formulation based on pharmacokinetic of sildenafil citrate. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, and drug content. The tablets were subjected to various tests for physical parameters such as thickness, hardness and friability, and in vitro release studies. Release kinetics was evaluated by using United States Pharmacopeia (USP)-22 type II dissolution apparatus. The in vitro dissolution study was carried out for 12 hours. In 0.1 N hydrochloric acid (pH 1.2) for first 2hrs followed by phosphate buffer at pH 7.4 ±0.2 for remaining 10 hours. The results of dissolution studies indicated that formulations containing natural gum LBG and synthetic gum HPMC K100 showed better dissolution. The drug release data fit well to the zero order. Korsmeyer's plot indicated that the drug release mechanism from the matrix tablet followed was Anomalous (non-Fickian) diffusion. It (F-3) showed that no change in physical appearance, drug content or dissolution pattern after storage at 40^0C temperature and relative humidity 75% for 90 days.

Keywords: Sildenafil Citrate, Locust bean gum, Hydroxyl proply methyl cellulose K100, Tamarind seed polysaccharide, Wet granulation.

INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions. Conventional formulations are required to be administered multiple doses and therefore have several disadvantages.[1]

The primary benefit of a sustained release dosage form, compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug.[2,3]

Hydrophilic polymer matrix systems are widely used for designing oral sustained drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[4] The hydrophilic polymers selected for the present study were HPMC K100, Xanthan gum, Locust

bean gum, Ethyl cellulose, and Tsp. These polymers provide pH-independent drug release to oral dosage forms that can be used for formulating the sustained-release dosage forms.[5,6]

Activity limitation and dyspnoea are the primary symptoms of chronic obstructive pulmonary disease (COPD) and progress as the disease advances, contributing to reduced quality of life. Pulmonary arterial hypertension (PAH) is a common complication during the course of COPD and is an important predictor of mortality.[7] Endothelial dysfunction and decreased concentration of endothelial derived nitric oxide may play an important role in the development of PAH in patients having COPD.[8]

Sildenafil is an orally active, potent and selective inhibitor of phosphodiesterase type 5 (PDE5) Present throughout the body, PDE5 is found in high concentrations in the lungs. Inhibition of PDE5 enhances the vasodilatory effects of nitric oxide in pulmonary hypertension by preventing the degradation of cyclic guanosine monophosphate (cGMP), which promotes relaxation of vascular smooth muscle and increases blood flow. In animal models and human trials, sildenafil has been found to produce a relatively selective reduction in pulmonary artery pressure without adverse systemic hemodynamic effects. Inhibition of PDE5 by sildenafil may also enhance the platelet antiaggregatory activity of nitric oxide and inhibit thrombus formation.[9,10]

The elimination half- life of Sildenafil Citrate is between 3 to 4 hours. It has 40% oral bioavailability and it is readily absorbed from gastro intestinal tract. Based on these physico- chemical and biopharmaceutical properties, Sildenafil Citrate was selected as a drug candidate for developing sustained release tablet formulation. Sildenafil Citrate appears to be a useful alternative to traditional therapies for pulmonary hypertension. Sildenafil Citrate is effective in patients with more severe COPD.[11,12]

MATERIALS AND METHODS

Materials: Sildenafil Citrate were purchased from yarrow chemicals Mumbai, Xanthan gum, Locust bean gum, Microcrystalline cellulose were purchased from Research- Lab Fine Chem Industries, Mumbai. Magnesium stearate, talc, PVP, polyethelene glycol 4000 were purchased from SD Fine chemicals Ltd, Mumbai. TSP were purchased from local market.

Extraction of Tamarind Seed Polysaccharide:
To 20g of tamarind kernel powder, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 mints under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged at 5000 rpm for 20 mints. The supernatant was separated and poured into twice the volume of absolute ethanol by continuous stirring. The precipitate was washed with absolute ethanol, diethyl ether and and then dried at 50-60º C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range. The particle size range of 150-75 microns was used for preparation of tablets.[13]

Preparation of matrix tablets:
Tablet formulations were prepared by wet granulation method. A non-aqueous granulation process was adopted to prepare Sildenafil citrate tablets. Granules were prepared as follows. Proportion of excipients with drug was as given in Table 1. All ingredients were sifted through sieve no. 60. A solid dispersion of Sildenafil citrate with PEG was prepared by using melt method. All polymers was mixed with the above solid dispersion manually according to the formula. PVP K30 was dissolved in isopropyl alcohol and used for wet granulation of the final blend. The wet mass was passed through sieve no. 16 and wet granules were dried at 60°C in an oven for 30 minutes. Dried granules were sized by passing it through sieve no.20 and lubricated with magnesium stearate and talc for 1 minutes. Tablets were compressed using Rotary tablet machine with 12.1 mm flat-shaped punches. Tablet weight was (600mg) kept constant as shown in table 1.

Evaluation of granules:
The angle of repose was measured by using funnel method which indicates the flow ability of the granules.[14] Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder /volume of the packing.[15] TBD= weight of the powder /tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)]

×100.[16] The physical properties of granules were shown in Table 2.

Evaluation of tablets:
All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods[17] shown in Table 3.

Uniformity of drug content:
Accurately weighed quantity of the powder tablet equivalent to 100 mg of the drug was transferred to 100 ml volumetric flask. 50 ml of buffer solution of pH-7.4 was added. Mix with the aid of ultrasound for 10 min, and then the volume was made up to 100 ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45µm. 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under UV Spectrophotometer at 292 nm.

Characterization of Drug Release Kinetics:
To study the release kinetics, data obtained form *in vitro* drug release studies were plotted in various kinetic models: zero order (equation 1), as the cumulative percentage of drug release Vs time, first order (equation 2), as the log of the amount of drug remaining to be released Vs. time and Higuchi model (equation 3), as the cumulative percentage of drug release Vs. square root of time.

$C = K\ t\ o$ (equation 1)

$Log\ C = Log\ C_0 - K_1\ t/\ 2.303$ (equation 2)

$Q = K_h t^{1/2}$ (equation 3)

The Korsmeyer and Peppas equation is: $Mt/M = kt^n$. Where M_t/M is the fraction of drug released at time t, k is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is an exponent used to characterize the transport mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $0.45 < n < 0.89$ for anomalous behavior or non-Fickian transport, $n = 0.89$ for Case II transport, and $n > 0.89$ for Super Case II transport. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion.[18,19]

Table 1: Tablet composition of different formulations of Sildenafil citrate sustained release matrix tablets with natural and synthetic polymers

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	40	40	40	40	40	40	40	40	40	40	40	40
LBG	50	100	200	-	-	-	-	-	-	200	200	200
Xanthan gum	-	-	-	-	-	-	-	-	-	-	-	-
Ethyl cellulose	-	-	-	50	100	200	-	-	-	-	-	-
HPMC K100	50	100	200	50	100	200	50	100	200	200	200	200
TSP	-	-	-	-	-	-	50	100	200	-	-	-
Lactose	-	-	-	-	-	-	-	-	-	82		-
Starch 1500	-	-	-	-	-	-	-	-	-	-	82	
DCP	-	-	-	-	-	-	-	-	-	-	-	82
PEG	30	30	30	30	30	30	30	30	30	30	30	30
MCC	82	82	82	82	82	82	82	82	82			
PVP	30	30	30	30	30	30	30	30	30	30	30	30
Magnesium Stearate	12	12	12	12	12	12	12	12	12	12	12	12
Talc	6	6	6	6	6	6	6	6	6	6	6	6

Table 2: Granular properties of formulations F1 to F12 of Sildenafil Citrate sustained release matrix tablets using natural, synthetic polymers and fillers as release retardant

Formulation No.	Angle of repose	Loose bulk density (LBD)(g/ml)	Tapped bulk density(TBD)(g/ml)	Compressibility index(%)
F1	31.27 ±1.38	0.235 ± 0.006	0.282 ± 0.015	16.65 ± 0.61
F2	32.25 ± 1.71	0.236 ± 0.02	0.267 ±0.036	11.61
F3	29.12 ± 1.67	0.273 ± 0.05	0.299 ± 0.02	8.69 ± 0.44
F4	28.15 ±1.35	0.265 ± 0.001	0.317 ± 0.018	16.40± 1.41
F5	30.84 ± 1.87	0.317± 0.007	0.367±0.010	13.12± 1.26
F6	28.26 ± 1.44	0.245 ± 0.07	0.275 ± 0.02	10.90 ± 0.78
F7	28.43 ± 1.43	0.228 ± 0.09	0.259 ± 0.01	11.96 ± 0.44
F8	29.87 ± 1.36	0.262 ± 0.006	0.295 ± 0.016	12.18 ± 0.78
F9	30.16 ± 1.25	0.256 ± 0.006	0.282 ± 0.015	9.21 ± 0.61
F10	27.52 ± 1.14	0.256 ± 0.006	0.282 ± 0.015	9.21 ± 0.61
F11	28.36 ± 1.42	0.203 ± 0.07	0.236 ± 0.07	13.98 + ± 1.23
F12	26.79 ± 1.25	0.221 ± 0.06	0.267 ± 0.08	16.63 ± 0.20

Table 3: Tablet properties of formulations F1 to F12 of Sildenafil Citrate sustained release matrix tablets with natural, synthetic polymers and fillers

Formulation No.	Thickness(mm)	Hardness(kg/cm^2)	Friability (%)	Drug content (%)
F1	3.89± 0.36	6.2 ± 0.25	0.29 ± 0.12	98.9 ± 0.20
F2	4.16± 0.08	6.5 ± 0.12	0.32 ±0.42	98.86 ± 0.124
F3	4.24± 0.03	6.5 ± 0.34	0.28 ± 0.34	99.7 ± 0.11
F4	3.71± 0.16	6.0 ± 0.1	0.24 ± 0.1	99.69 ± 0.14
F5	4.42 ± 0.014	6 ± 0.02	0.28 ± 0.2	99.65 ± 0.16
F6	4.0 ± 0.024	6.2 ± 0.4	0.28 ± 0.37	99.60 ± 0.24
F7	3.41 ± 0.28	6.2 ± 0.04	0.33 ± 0.061	99.67 ± 0.14
F8	4.06 ± 0.08	6.4 ± 0.04	0.37 ± 0.020	99.88 ± 0.234
F9	4.26 ± 0.18	6 ± 0.12	0.25 ± 0.021	99.54 ± 0.22
F10	3.57 ± 0.14	6.5 ± 0.13	0.37 ± 0.21	99.22 ± 0.12
F11	4.34 ± 0.0.25	6.3 ± 0.35	0.23 ± 0.6	99.97 ± 0.131
F12	4.02 ± 0.12	6.4 ± 0.05	0.32 ± 0.24	99.80 ± 0.04

Figure: 4. Correlation coefficients of different mathematical models for formulations F- 1 to F-3, F-5, F-6, F-8 to F-12

Formulation No.	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R^2	Slope n
F1	0.987	0.868	0.998	0.996	0.703
F2	0.994	0.661	0.963	0.973	0.637
F3	0.997	0.675	0.978	0.987	0.701
F5	0.970	0.712	0.920	0.925	0.648
F6	0.997	0.692	0.975	0.975	0.640
F8	0.992	0.868	0.999	0.999	0.640
F9	0.999	0.715	0.976	0.987	0.656
F10	0.936	0.530	0.972	0.979	0.672
F11	0.906	0.583	0.981	0.988	0.689
F12	0.904	0.568	0.977	0.984	0.688

Stability Study:

The optimized formulation was subjected to stability at 25^{o}C± 2^{0}C / 60% ± 5% RH, 30^{0}C ± 2^{0}C / 65% ±5% RH and 40^{0}C ± 2^{0}C / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile.[20]

RESULTS AND DISCUSSION

FTIR spectroscopy:

The FT-IR Spectrum of pure Sildenafil citrate and its physical mixture with polymers and different excipients are shown in Figure: 1 - 7 . Pure Sildenafil citrate showed peaks at 3294.117 cm-1 (O-H stretch), 1697.612 cm-1 (N-H bend), 1562.947 cm-1 (N-O asymmetric bend), 1458.577 cm-1 (C-H bend), 1357.714 cm-1 (C-H rock), 1278.632 cm-1 (C-O stretch), 1027.094 cm-1 (C-N stretch), 939.192 cm-1 (O-H bend). Infrared absorption spectrum of formulation F-3, F-6, F-9, F-15 20 showed peaks at at 3295.534 cm-1 (O-H stretch),

1699.512 cm-1 (N-H bend), 1562.156 cm-1 (N-O asymmetric bend), 1458.696 cm-1 (C-H bend), 1358.999 cm-1 (C-H rock), 1279.685 cm-1 (C-O stretch), 1026.998 cm-1 (C-N stretch), 940.337 cm-1 (O-H bend).

Infrared spectra of drug and polymers were used to study the compatibility between them. No change in peak shows that there was no interaction between drug and polymers. The IR spectrum of the pure drug (Sildenafil Citrate) and optimized formulation F3 is given in figure 1-2.

SEM studies of the optimized formulation F3

The Scanning Electron Microscopic (SEM) Analysis was conducted using a JOEL (Model - JSM 840A) Scanning Microscope for the optimized formulations in three states involving dry tablet surface, Tablet after swelling for 2 hours and Tablet after swelling for 6 hours and 12hours, so as to determine particle size distribution, surface topography, and texture and to examine the morphology of fractured or sectioned surfaces.

SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix. SEM photomicrographs with graphs of tablet surface at different time intervals also showed that erosion of matrix increased respect to time indicated by the photomicrographs at 2, 6, and 12 hours revealing pores with increasing diameter. These photomicrographs also revealed formation of gelling structure. Hence, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Sildenafil Citrate from formulated matrix tablets.

DSC STUDY:

According to the thermo grams, Sildenafil Citrate presented a sharp endothermic peak at 197.13ºC corresponding to the melting point of the drug in the crystalline form. While the thermo gram of physical mixture of Sildenafil Citrate, locust bean gum and hydroxyl proply methyl cellulose K100 was 151ºC. The comparative study of thermograms indicated that the drug even in its drug mixture sample form has not much deviated from the literature melting point 189-190ºC[12]appreciably indicating that the drug has not undergone any type of interaction with the polymer used for the formulation. It is also clear that the drug has not undergone any type of interaction with the polymer used in the formulation from the FTIR reports. The spectra of the DSC are shown in Figure 9-10.

Characterization of granular properties

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Tables 2. Angle of repose was in the range 26.79 ± 1.25 to 32.25 ± 1.40, which indicates excellent flow of the powder for all formulations. The bulk density of the powder formulation was in the range of 0.203 ± 0.07to 0.317± 0.007gm/cc, the tapped density was in the range of 0.236 ± 0.07to 0.367±0.010gm/cc, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 8.69 ± 0.44 to 16.65 ± 0.61 indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Physicochemical evaluation of matrix tablets

Tablets with a weight of 600 mg were subjected to quality control tests such as thickness hardness, friability and drug content (Table 3). The contents of the formulations were found to be uniform, since the amount of the active ingredient in each of the10 units tested was within the range of 98.86 ± 0.124 to 99.97 ± 0.131 and the relative standard deviations were less than 2.0% indicating uniform mixing of polymers and drug. The mean values for hardness were over 6.0 kg/cm2 and all formulations exhibited a friability of not more than 0.6% during the friability determination. The punches used to compress the tablets were 12.1 mm spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 6 ± 0.02 to 6.5 ± 0.12 Kg/cm^2. It was within the range of monograph specification. Thickness of the tablets was found to be in the range of 3.57 ± 0.14 to 4.42 ± 0.014. The friability of the tablets was found to be less than 1% and it was within the range of standard specification.

***In-Vitro* Release Study**

In- vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing rotating paddle at 50 rpm. The dissolution medium consist of 750ml of 0.1N Hcl (1.2 pH)for 2 hours and then the pH was changed to 7.4 by adding 250 ml of 0.2 m Tri sodium phosphate for rest of the dissolution duration. The temperature was maintained at 37±5^{0}C through out the experiment. 5 ml of sample was withdrawn at predetermined

time interval replacing with equal quantity of drug free dissolution fluid. The sample withdrawn were filtered through 0.45µm membrane filter and drug content in each sample was analysed after suitable dilution by UV/Visible spectroscopy at 292nm.

The results were evaluated for 12 hr. As per the results of dissolution study formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12 showed 99.68, 98.48, 99.24, 99.28, 98.76, 99.1, 99.34, 99.6, 98.76, 99.15, 99.86, 99.62 respectively.

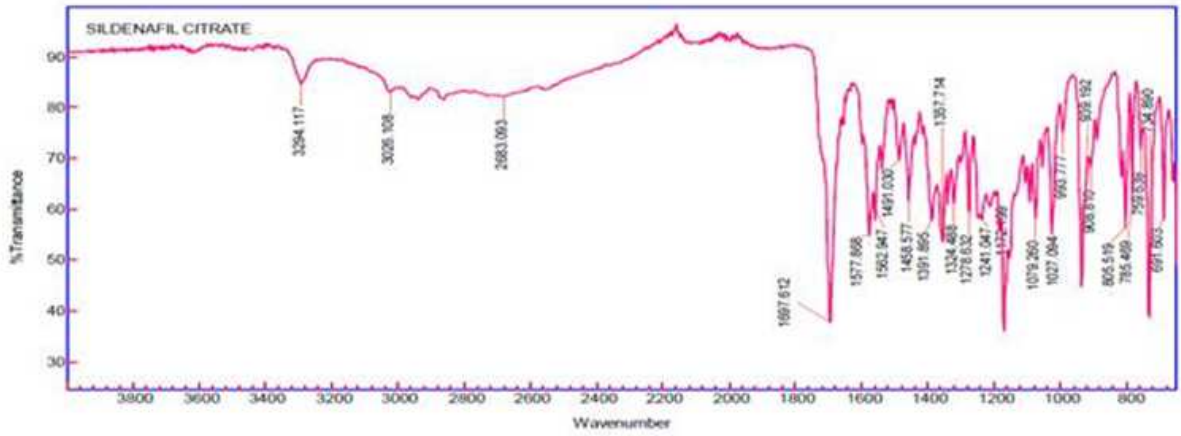

Figure:1. FTIR Spectroscopy of pure drug (Sildenafil Citrate)

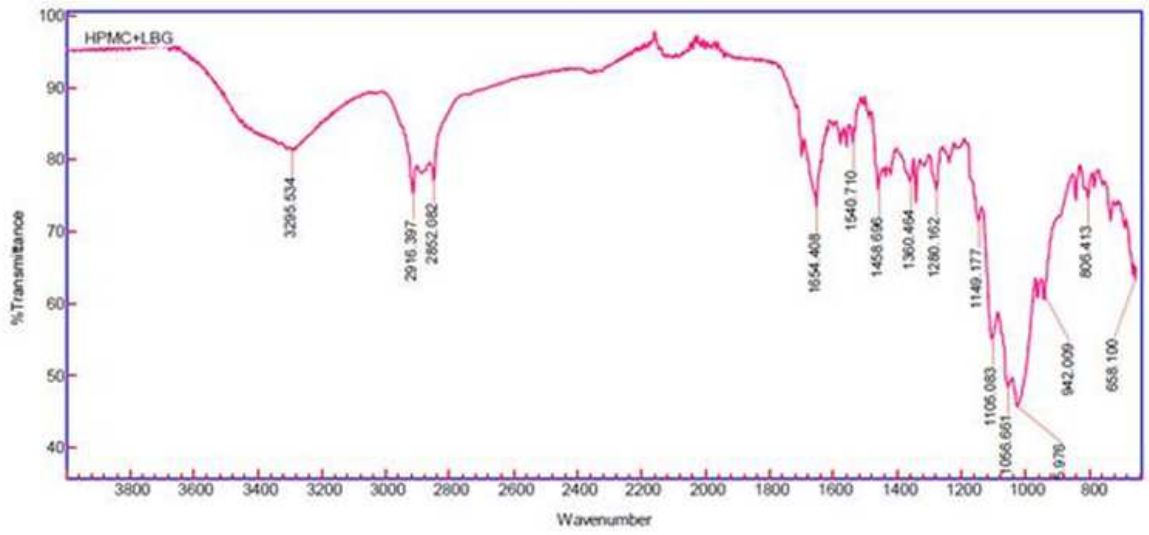

Figure:2. FTIR Spectroscopy of formulation (F-3)

Incorporation of locust bean gum along with HPMC K 100 in the formulation F-1 to F-3 showed better retarded the release rate of drug compared to all other formulations and drug release was decreased with increased polymer concentration. This might be due to quick hydration on the outer layer of tablet and gelatinous layer formation character of HPMCK100, the involvement of synergism between LBG and HPMC K100 gum is also the reason for the decrease in drug release. Formation of a gel layer was obtained from the interaction between the above two polymers.

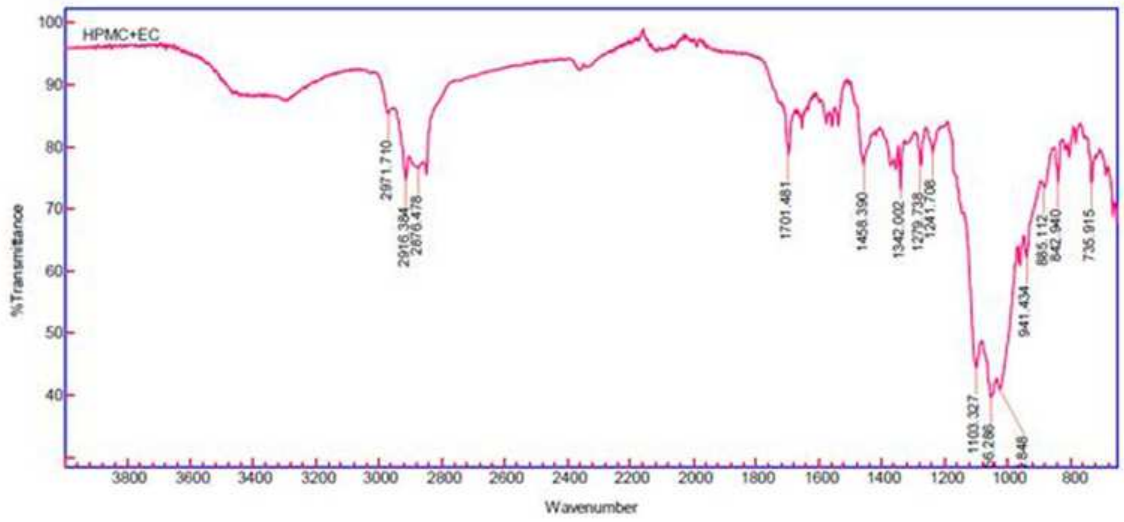

Figure:3. FTIR spectroscopy of formulation (F-6)

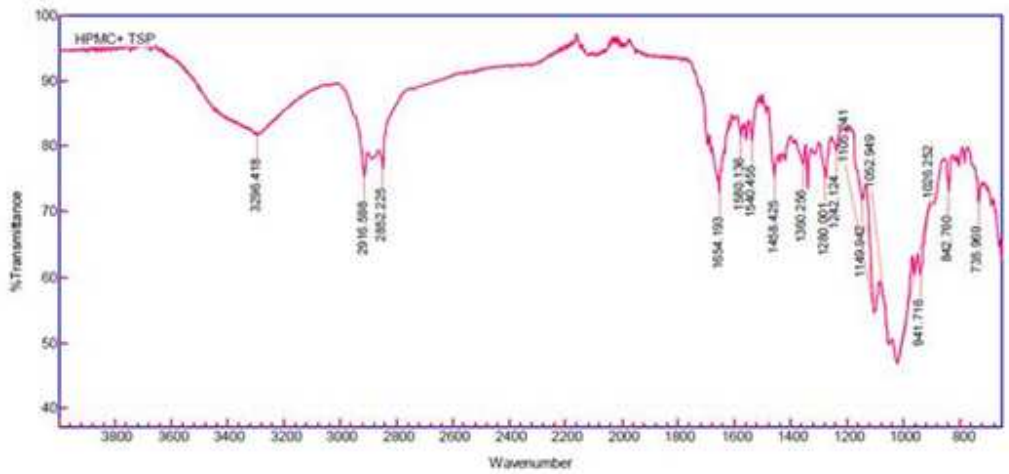

Figure:4. FTIR spectroscopy of formulation (F-9)

F4 to F6 When the polymer concentration of HPMC K100 and Ethyl cellulose increased the drug release rate was reduced from the above formulations. This might be due to quick hydration on the outer layer of tablet and gelatinous layer formation character of HPMCK100 and from ethyl cellulose is probably due to less water permeability character.

Tablets F-7 to F-9 decrease in drug release was observed with higher concentration of polymers (HPMC K 100 and Tamarind seed polysaccharide). This might be due to quick hydration on the outer layer of tablet and gelatinous layer formation character of HPMCK100 and hydration, swelling and gelatinous layer formation nature of Tamarind Seed Polysaccharide.

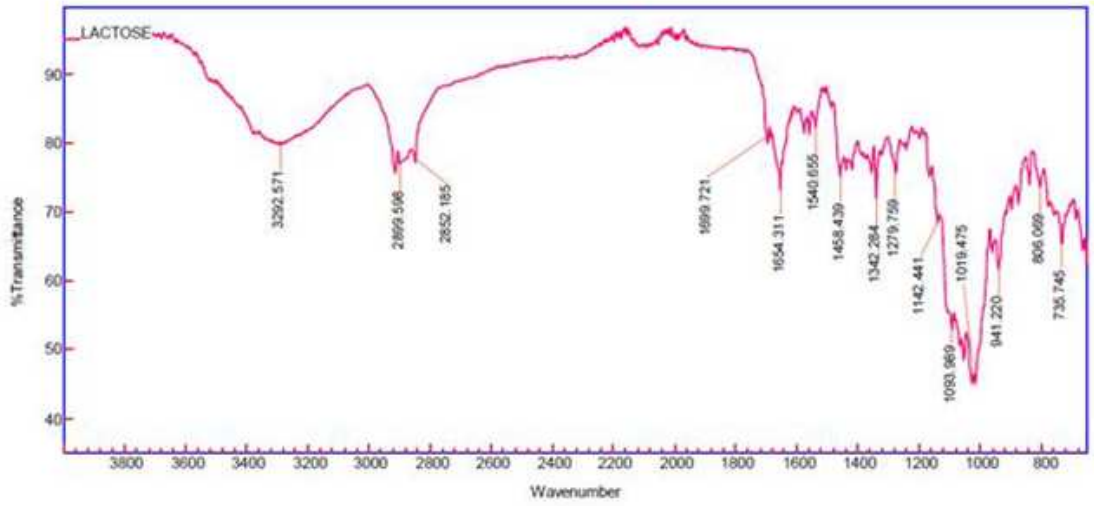

Figure:5. FTIR spectroscopy of formulation (F-10)

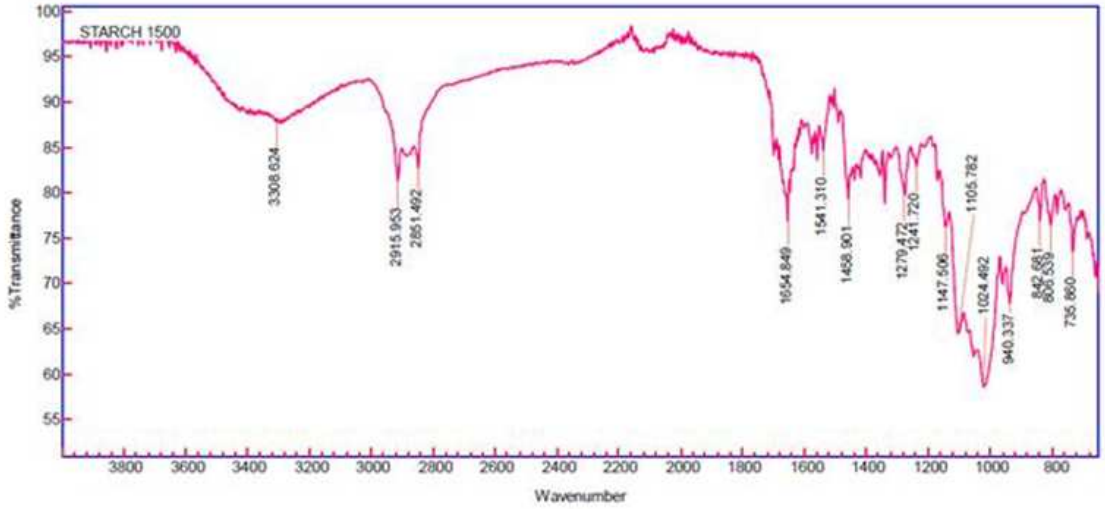

Figure:6. FTIR spectroscopy of formulation (F-11)

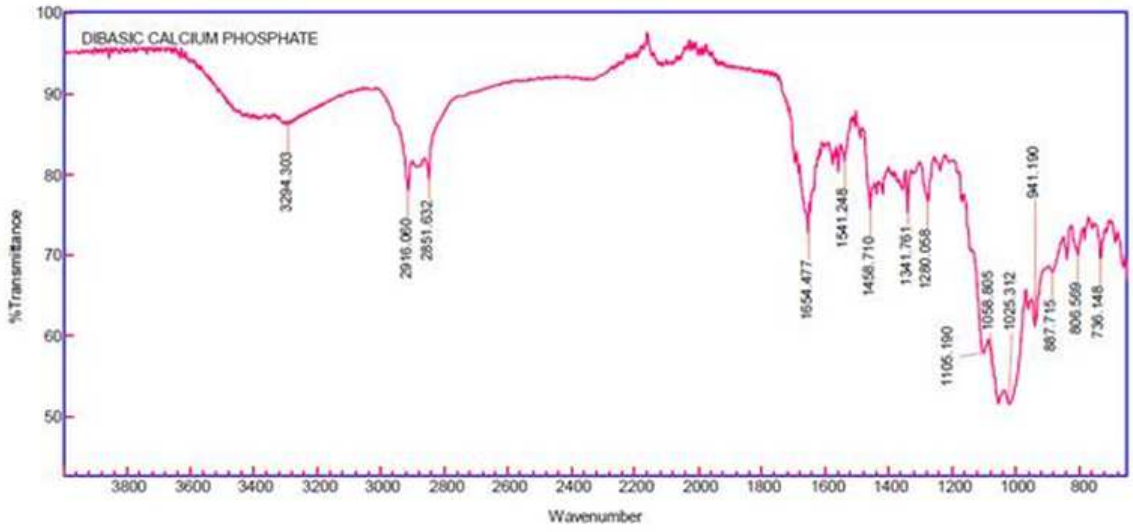

Figure:7. FTIR spectroscopy of formulation (F-12)

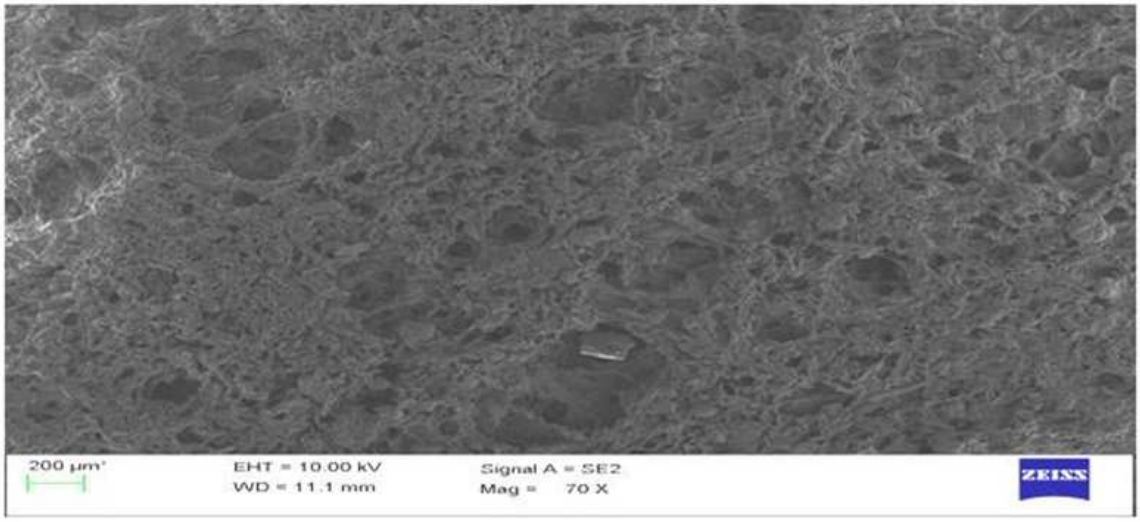

Fig (a) 2 th hour

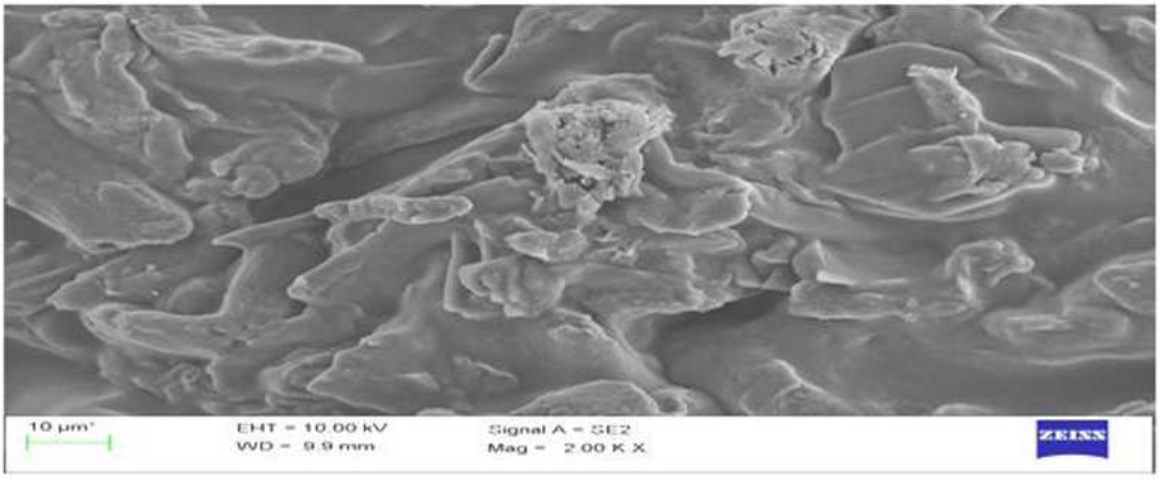

Fig (b) 6 th hour

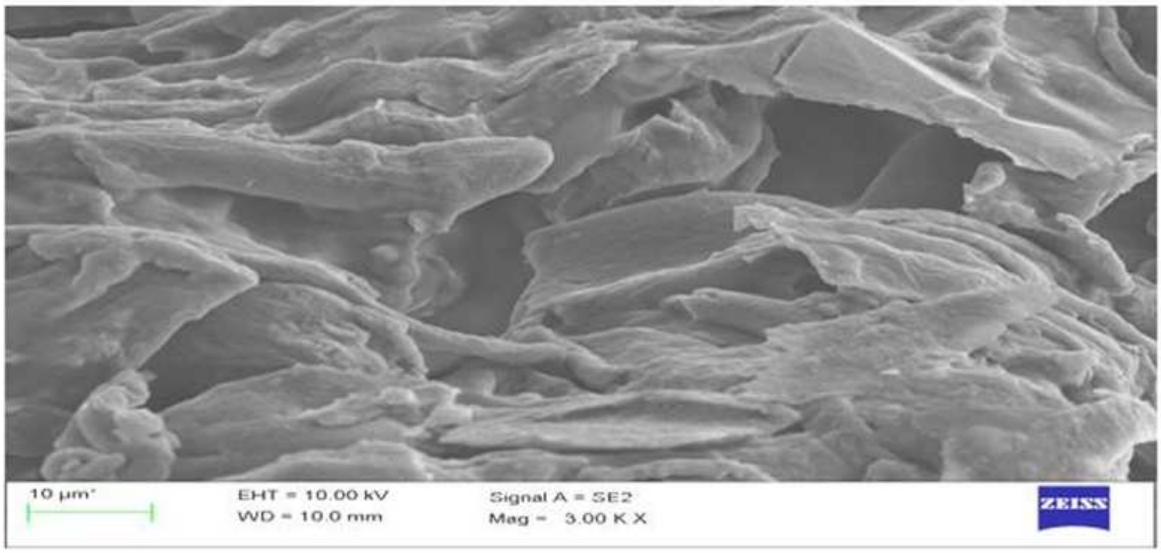

Fig (c) 12 th hour

Figure:8. SEM photomicrographs at the end of 2, 6, and 12 th hour

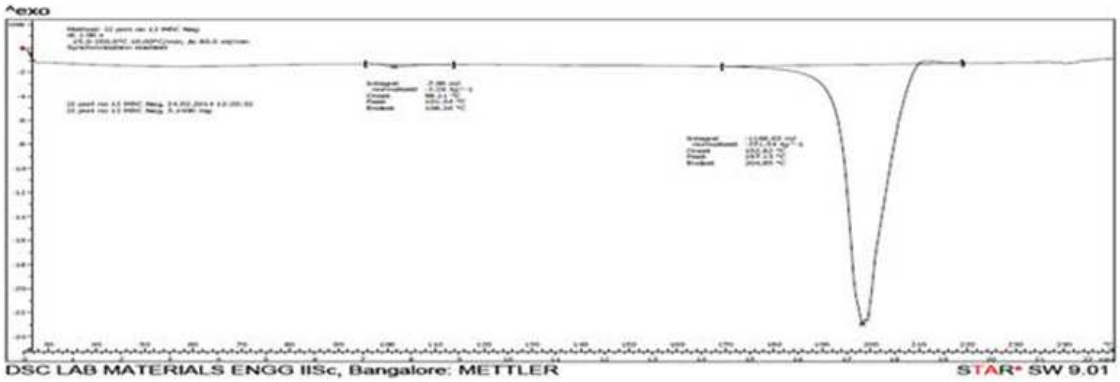

Figure: 9. DSC thermogram of pure sildenafil citrate

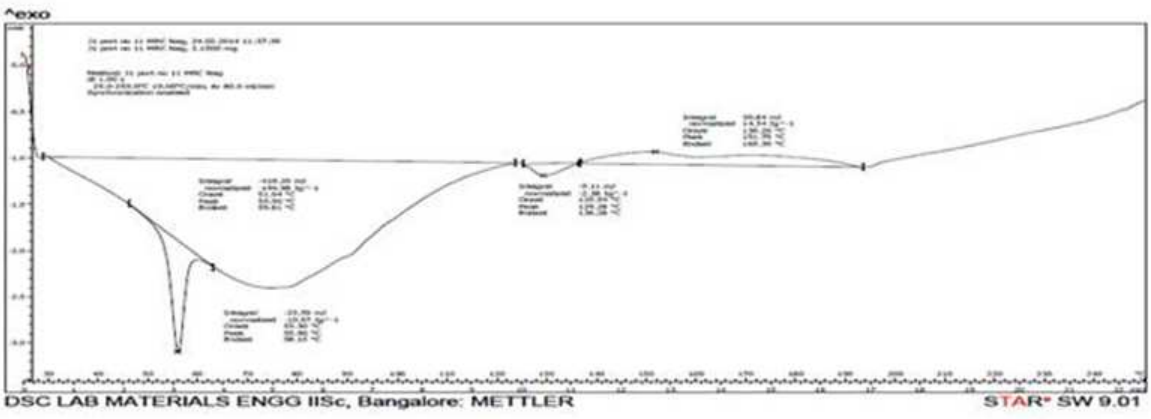

Figure:10. DSC thermogram of optimised formulation F-3

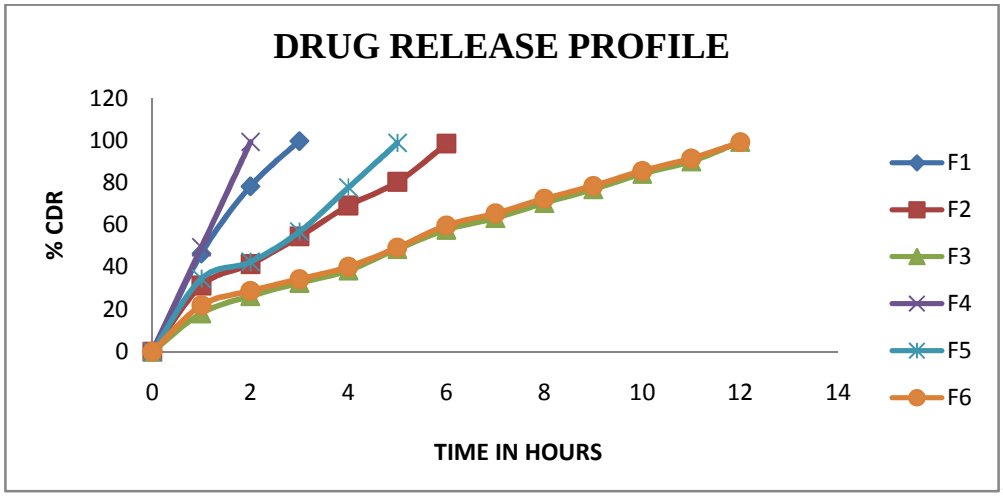

Figure:11. *In Vitro* Dissolution Profile of F-1 to F-6 Formulations

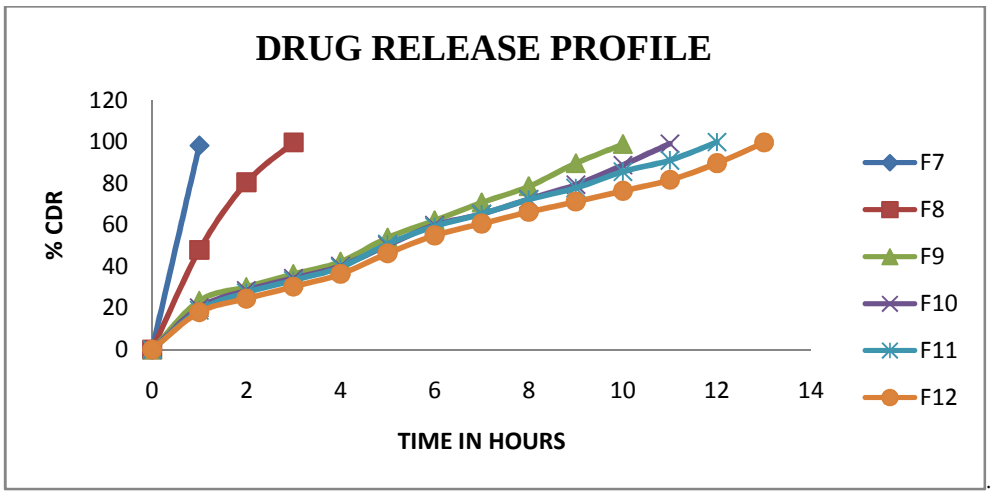

Figure:12. *In Vitro* Dissolution Profile of F-7 to F-12 Formulations

Determination of the release kinetics

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F-1 to F-12 could be best expressed by zero order equation as the plots showed highest linearity (R^2: 0.904 to 0.999), than first order release kinetics (R^2: 0.530 to0.895). The n values obtained from Korsmeyer Peppas plots range from (0.637 to 0.703) indicate that mechanism of release of formulations F-1 to F-12 was Anomalous (non-Fickian) diffusion.

CONCLUSION

The matrix tablets were found to be effective in sustaining the drug release upto 12 hr. This is mainly due to formation of a thick gel structure that delays drug release from tablet

Matrix. Drug release was found to be diffusion coupled with erosion. Stability studies revealed that there was no significant change in drug content and dissolution profile of matrix tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Sildenafil Citrate and other ingredients used. SEM studies revealed that the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Sildenafil Citrate from formulated matrix tablets. It can be concluded that stable formulation could be developed by incorporating natural and synthetic polymer in a definite proportion, so that the sustained released profile is maintained for an extended period.

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