ISSN: 0975-766X
CODEN: IJPTFI
Research Article

Available Online through
www.ijptonline.com

FORMULATION AND EVALUATION OF SUSTAINED RELEASE BILAYERED MATRIX TABLETS OF SILDENAFIL CITRATE

Mohammed Asif Hussain[1], Krishnakanth jadhav[1*], Maimuna Anjum[1]
Blue Birds college of Pharmacy, Bheemaram (v), Hanamkonda-506 015, A.P, India.
Email: krishnakanth.jadhav@gmail.com

Received on 22-12-2013 *Accepted on 19-01-2014*

Abstract

Sildenafil citrate is a selective inhibitor of phosphodiesterase type 5 enzyme (PDE5), it offers potential to treat patients with pulmonary hypertension by selectively inhibiting PDE type five pathways in the lung. It is recommended for selected patients with pulmonary arterial hypertension, and has favourable effects on endothelial function. Sustained release bilayer matrix tablets of Sildenafil citrate is designed by simplex lattice design and evaluating the relationship and influence of different content levels of HPMC (Hypromellose), Carbopol (Carbomer) and Xanthangum in order to achieve a first-order release of Sildenafil citrate. Tablets were prepared by wet granulation process and evaluated for different pre and post compression parameters; from these matrix tablets drug release was prolonged, leading to achieve an effective therapy with low dosage of the drug, to reduce the frequency of medication.

Keywords: Sildenafil citrate, Bilayer Matrix tablet, HPMC, Carbopol, Xanthan gum, Pulmonary Hypertension.

Introduction[1,2]:

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and have traditionally prepared by either compression, or molding methods.Oral route is the most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product.Even for sustained release systems the oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers.With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-toxic for an extended period of time. To achieve better therapeutic action various types of drug delivery systems are available, out of which sustained

release systems are gaining much importance because of to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance.

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

Pulmonary arterial hypertension(PAH) is defined as an elevation of the mean pulmonary arterial pressure (PAPm) above 25 mmHg at rest and/or above 30 mmHg during exercise in the setting of normal or reduced cardiac output and normal PCP.

Sildenafil citrate is a selective inhibitor of phosphodiesterase type 5 enzyme (PDE5), it offers potential to treat patients with pulmonary hypertension by selectively inhibiting PDE type five pathways in the lung. It is recommended for selected patients with pulmonary arterial hypertension, and has favourable effects on endothelial function.

Typical adverse reactions of Sildenafil citrate in adult patients include flushing, headache and dyspepsia.The use of organic nitrates is however contraindicated with Sildenafil citrateuse, as sildenafil enhances the vasodilatory effects of the nitrates, which can lead to excessive vasodilation followed by a significant decrease of blood pressure.

Sildenafil citrate is a selective inhibitor of the phosphodiesterase type 5 enzyme that is found in high concentrations in the pulmonary vascular smooth muscle. PDE5 enzymes are responsible for the hydrolysis of (cGMP) to form guanosine 5'-cyclic phosphate. cGMP is a secondary messenger of nitric oxide (NO). NO is a vasodilator and hence an increase in cGMP will lead to an increase in NO, thereby promoting vascular smooth muscle relaxation.

The main objective of present study is to develop Bilayer matrix tablets of Sildenafil citrate for the treatment of pulmonary hypertension.

To study the effect of various factors like

1) Drug polymer ratio:In the present study different grades of HPMC polymers such as K100M, K15M and K4Min various ratios are used.

2) Effect of Combination of Polymers**:**In the present investigation three grades of HPMC polymers i.e, K100M, K15M and K4M are used in combination with carbopol and xanthan gum the duration of drug release rate was carefully evaluated.

Materials and Methods:

Materials:

Sildenafil citrate is a gift sample from A.P drugs control office, Hyderabad. Hydroxy propyl methyl cellulose (HPMC K100M, HPMC K15M, HPMC K4M non-ionicpolymers) was donated by SD Fine chemicals, Mumbai, India.Carbopol 940 (anionic polymer) was purchased from Himedia laboratoriesand Xanthangum was purchased from SD Fine chemicals, Mumbai, India. Microcrystalline cellulose was purchased from Universal laboratories. All otherchemicals and reagents used from INR chemicals.

Formulation of Bi-Layer Tablets:

The bilayer tablets of Sildenafil citrate were prepared by the wet granulation method. The drug and polymers for both IR and SR layer were passed through a # 60 sieve before their use in the formulation.In the present study bilayer tablet was prepared manually using single station punching machine. Accurately weighed amount of SR powder mix was fed manually into die cavity. SR layer was compressed at mild compression force. After that accurately weighed IR powder mix was manually fed into the die on SR layer and compressed using 9-mm flat punches. Formulations are shown in detail in table 1 and 2.

Table no.1: Formulation development of Sildenafil citrate IR layer.

S.no	Ingredients	Formula(mg)
1	Drug	8
2	Sodium starch glycolate	5
3	Microcrystalline cellulose	24
4	Mg.stearate	3
5	1.5% PVP	q.s

- Total weight of immediate layer is 40 mg.

Table no.2: Formulation development of Sildenafil citrate SR layer.

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	17	17	17	17	17	17	17	17	17	17	17	17
HPMC K100M	15	25	12.5	12.5	---	---	---	---	---	---	---	---
HPMC K15M	---	---	---	---	25	30	15	15	---	---	---	---
HPMC K4M	---	---	---	---	---	---	---	---	40	50	25	25
Carbopol	---	---	12.5	---	---	---	15	---	---	---	25	---
Xanthangum	---	---	---	12.5	---	---	---	15	---	---	---	25
MCC	171	161	161	161	161	156	156	156	146	136	136	136
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Mg.stearate	3	3	3	3	3	3	3	3	3	3	3	3
1.5% PVP	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

- Total weight of controlled release layer is 210 mg.
- Total Tablet weight in all formulation is 250 mg.

Evaluation of Bilayer Tablets:

All the prepared Bilayer tablets were evaluated for following parameters.

Determination of physicochemical parameters of tablets:-

1) Weight Variation[3]: Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets were calculated. Then each batch passes the weight variation test if not more than two of the individual tablet deviate from the average weight by more than the percentage.

2) Thickness[3]: Ten tablets were selected randomly from each batch and thickness was measured by using verniercalipers.

3) Hardness[4]: Hardness was measured by using Pfizer apparatus. For each batch five tablets were tested. The force is measured in kilograms.

4) Friability[5]: The Roche friability test apparatus was used to determine the friability of the Tablets. Three pre-weighed Tablets were placed in the apparatus and was rotated at 25 rpm for 4 minutes and then the Tablets were reweighed. The percentage friability was calculated according to the following formula.

% friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where W_1 = Initial weight of the 10 tablets.

W_2 = Final weight of the10 tablets after friability.

Friability values below 1.0% are generally acceptable.

5) Drug content (assay)[3]:

Three tablets were taken and powdered. Powder equivalent to one tablet was taken and dissolved in 50 ml of pH 7.4 phosphate buffer. The mixture was allowed to stand for 1 hrwith intermittent sonication to ensure complete hydration of polymer and subsequent solubility of the drug. Then the volume was made up to 100ml.The mixture was filtered and 1ml of the filtrate was suitably diluted. The absorbance of solution was measured by using UV – Visible spectrophotometer (Elico, India) at 291nm. Each measurement was carried out in triplicate and the average drug content in the bilayer tablet was calculated.

6) *In –vitro* Dissolution studies[3]:

The *In-vitro* dissolution study was conducted using rotating paddle method to study the drug release from the tablet. The tablet is placed in basket. The dissolution medium consisted of 900 ml of acid buffer (pH1.2) for first two hours, phosphate buffer (pH7.4) for next ten hours. The release was performed at 37°C ± 0.5°C, at a rotation speed of 50 rpm. 5ml samples were withdrawn at predetermined time intervals (1 to 12hrs) and the same volume was replaced with fresh medium. The samples werefiltered through Whattman filter paper and analyzed by UV spectrophotometer at 291 nm. The percentage drug release was calculated using the calibration curve of the drug in (pH1.2) acid buffer and (pH7.4) phosphate buffer.

7) Drug release kinetics and mechanism:

To analyze the mechanism of drug releasefrom the formulation, the dissolution profile of all thebatches were fitted to zero order, first order, Higuchiand Peppasmodels to ascertain the kinetic modelling of drug release.

- **Zero Order[6]:** $Q = K_0 t$

Where, Q is the amount of drug release at time, t and Kois the release rate constant.

- **First order[7] :** $\text{Log } Q_t = \text{Log } Q_o + K_1 t / 2.303$

Where Q_t is the amount of drug released in time t, $Q_o$is intial amount of drug in the solution and K_1 is the first order release rate constant. In this way a graphical relationship between log percent drug remaining versus time to get the first order constant from the slope.

- **Peppas model[8] :** $Mt/M\infty = kt^n$

Where, $Mt/M\infty$ is fraction of drug released at time‘t’, k represents a constant, and n is the diffusionalexponent, which characterizes the type of releasemechanism during the dissolution process. For nonfickianrelease, the value of n falls

between 0.5 and1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and forsuper case II transport, n > 1.

- **Higuichi model**[9] **:** $Q = K_2 t^{1/2}$

Where, Q is the percentage of drug release at time t and K_2 is the diffusion rate constant.

8) Similarity Factor (f2) Analysis

In vitro release profiles of sustained release tablets were compared with the theoretical release profile which was calculated earlier. The data were analyzed by the following formula.

$f_2 = 50 \log \{[1+ (1/N) \sum (R_i - T_i)^2]^{-0.5} \times 100\}$

Where N = number of time points, Ri and Ti = dissolution of reference and test products at time i. If f_2 is greater than 50 it is considered that 2 products share similar drug release behaviors.

9) Fourier Transform infrared (FTIR) Spectroscopic studies:

Fourier Transform Infrared spectrophotometer (FTIR) was used for infrared analysis of samples to intercept the interactions of drug with polymers and other ingredients. The powder sample along with KBr was used for FTIR studies. The samples were analyzed between the wave numbers 4000 and 400 cm^2.

Results and Discussion:

Discussion:

The Pre formulation studies were performed and the results were shown in table no.3. Bulk density was found in the range of 0.32-0.47 g/cm^3 and the tapped density between 0.38-0.56 g/cm^3. Using these two density data compressibility index was calculated. The compressibility index was found between 10.53–18.54 and the compressibility flowability correlation data indicated a fairly good flowability of the blend. Angle of repose was found to be in the range of 22.88- 29.93 indicating excellent flowability, hausner's ratio in range of 1-1.225 indicating good flow ability.

The tablets of different formulations were subjected to various evaluation tests such as weight variation, hardness, thickness, friability and drug content. In weight variation test, the pharmacopeial limit of percentage deviation for the tablets of 130-324 is ±7.5%. The average percentage deviation of all the formulations was found to be within the limits. The hardness ranged from 5.8 ± 0.28 to 7.8 ± 0.28 kg/cm^2 . The thickness of tablets ranged from 3.39 ± 0.06 to 3.66 ± 0.04 mm. The friability was below 1% for all the formulations, which is an indication of good mechanical

resistance of the tablets. The drug content was found to be uniform in all formulations and ranged from 95.66 ± 0.08 to 104.8 ± 1.17. The detail of Physico-chemical parameters of all the formulations is shown in table no. 4.

A) Evaluation of pre-compression parameters of Tablets:

Table no.3: Results for Derived and Flow properties

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±S)	Hausner's ratio (mean±SD)
F1	0.46±0.00	0.53±0.01	26.79±1.15	14.16±0.03	1.153±0.02
F2	0.41±0.01	0.49±0.02	25.86±0.22	18.54±0.03	1.196±0.03
F3	0.47±0.01	0.52±0.01	27.06±1.01	10.54±0.01	1.107±0.05
F4	0.47±0.01	0.56±0.01	22.88±1.08	10.53±0.01	1.192±0.02
F5	0.45±0.00	0.48±0.03	26.37±1.17	14.85±0.04	1.067±0.03
F6	0.38±0.03	0.38±0.00	27.50±0.99	16.13±0.05	1.000±0.04
F7	0.32±0.02	0.38±0.02	28.21±0.29	13.54±1.19	1.187±0.02
F8	0.45±0.01	0.56±0.01	24.87±0.40	11.69±3.61	1.125±0.05
F9	0.41±0.01	0.45±0.00	25.17±0.34	10.87±2.84	1.110±0.04
F10	0.44±0.00	0.52±0.03	26.78±0.63	14.21±1.11	1.182±0.01
F11	0.40±0.02	0.49±0.01	29.93±0.46	13.47±2.48	1.225±0.03
F12	0.46±0.02	0.53±0.01	28.21±0.27	14.23±3.22	1.152±0.02

B) Characterization of physicochemical parameters of Tablets:

Table no.4: Evaluation of physical parameters of the Tablets

Formulation Code	Weight Variation(mg)	Hardness (Kg/cm^2)	Thickness (mm)	Fraibility (%)	Drug content(%)
F1	246.8±4.13	5.8±0.28	3.49±0.05	0.79±0.04	100±2.5
F2	251.7±7.0	6.1±0.28	3.48±0.04	0.66±0.03	97.4±0.5
F3	249.3±5.31	5.8±0.28	3.51±0.06	1.00±0.00	104.8±1.17
F4	250.9±2.51	6.1±0.28	3.59±0.03	0.26±0.03	104±0.2
F5	249.3±3.65	6.8±0.28	3.42±0.04	0.40±0.05	95.66±0.08
F6	249.2±4.56	7.0±0.00	3.60±0.03	0.53±0.03	99.14±1.02
F7	248.2±6.23	6.5±0.50	3.39±0.06	0.94±0.01	100.88±2.51
F8	247±4.71	6.8±0.28	3.51±0.02	0.26±0.02	100±2.00
F9	247.7±4.29	7.8±0.28	3.53±0.05	0.60±0.04	103.4±3.32
F10	247.9±2.80	7.5±0.61	3.64±0.04	0.66±0.03	101.7±0.01
F11	248.1±2.46	7.5±0.86	3.66±0.04	0.40±0.05	104.36±1.0
F12	247.7±5.2	7.6±0.28	3.64±0.05	0.91±0.06	98.27±0.04

***In-Vitro* Drug Release Studies:**

Bilayered sustained release matrix tablets of Sildenafil citrate of all formulations were subjected to*In vitro*drug release studies in pH 1.2 for first two hours and pH 7.4 for next 10 hours. The cumulative percent of drug released at different time intervals are given in Figure 1& 2. IR layer of all the formulations showed the burst release of Sildenafil citrate within 10 minutes. Presence of superdisintegrant (sodium starch glycolate) in Immediate Release layer showed faster disintegration of the layer. This can be attributed to the extent of water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration.

D) *In vitro* drug release studies:

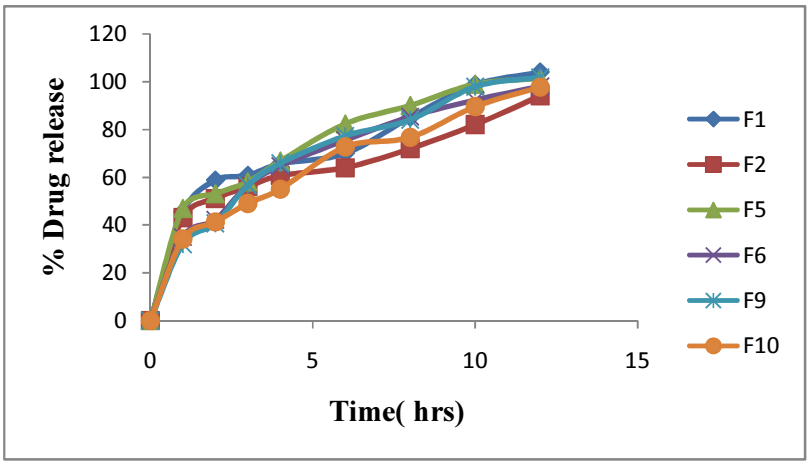

Fig no.1: Dissolution profile for matrix tablets of formulations F1, F2, F5, F6, F9, F10

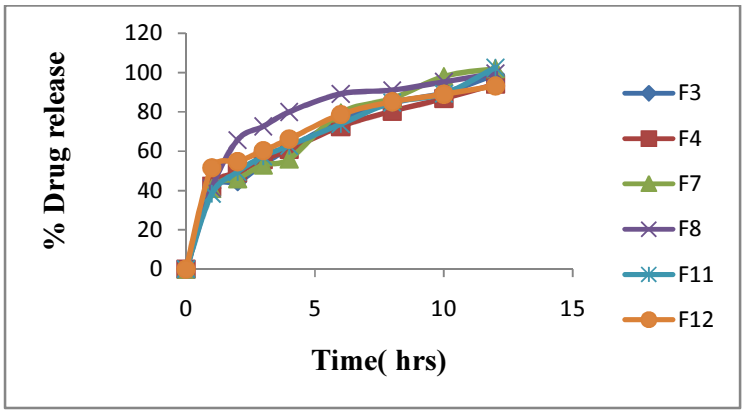

Fig no.2: Dissolution profile for matrix tablets of formulations F3, F4, F7, F8, F11, F12.

All the formulations of Sildenafil citrate showed the drug release upto 12hrs in controlled manner without changing their physical integrity in dissolution medium. The release of the drug at 12 hr varied from 93.2±0.17 to 104±0.22 % indicating that the overall drug release from the dosage form depends upon the composition of tablet matrix which

varies from one formula to another. The cumulative percentage drug release of the optimized formulation F10 was found to be 97.60 at the end of 12 hrs.

The data obtained from *invitro* dissolution studies were fitted to Zero order, first order, Higuchi and Korsmeyerpeppas equation and the results are shown in Table 6. The first order plots of F1 to F12 were found to be fairly linear as indicated by their high regression values when compared with zero order plots, so all the formulations followed first order kinetics.

All the formulations (F1 to F12) showed good correlation in Higuchi Kinetics, clearly indicating that the drug release mechanism was predominantly diffusion controlled. To confirm the exact mechanism of drug release from these tablets, the data were fitted to Korsmeyer equation. The slope values suggested that the release of Sildenafil citrate from formulations F1 to F12 followed fickian diffusion ($n<0.45$).

To compare the dissolution profile of each formulation with the theoretical release profile, the similarity factor (f2) values of the formulations (F1 to F12) were calculated. The f2 value of the formulations F2, F3, F4, F6, F7, F9, F10 and F11 was higher than 50 indicating that the drug release profile was similar to the theoretical release profile. Among them F10 formulation is the most optimized formulation based on its highest f2 value.All f2 value results are shown in table no. 5.

FTIR peaks obtained in the spectrum of formulation correlated with the peak of drug spectrum and there were no significant extra peaks, as shown in fig. no. 3 and 4.

C) Drug Release kinetics and Similarity factor (f2) Analysis Results:

Table no.5: Kinetic data of Formulations

Formulations	Zero order		First order		Peppas		Higuchi	Similarity factor (f2)
	R^2	K_0	R^2	K_1	R^2	N	R^2	
F1	0.7815	7.448	0.8008	0.337	0.9381	0.3032	0.9457	44.34
F2	0.7848	5.698	0.8846	0.180	0.9507	0.2896	0.9424	53.55
F3	0.8568	6.795	0.8669	0.308	0.9687	0.3819	0.9844	53.98
F4	0.8142	6.172	0.9686	0.202	0.9873	0.3328	0.9719	53.51
F5	0.8230	8.057	0.8894	0.380	0.9609	0.3413	0.9738	42.61
F6	0.8599	7.007	0.9534	0.287	0.9876	0.4349	0.9899	52.3
F7	0.8806	8.313	0.8936	0.334	0.9335	0.4003	0.9796	50.73

F8	0.6793	6.323	0.9091	0.370	0.9142	0.3234	0.9054	34.19
F9	0.8877	8.539	0.8934	0.324	0.9849	0.4928	0.9931	50.51
F10	0.8991	6.931	0.9072	0.262	0.9827	0.4386	0.9930	67.73
F11	0.8205	7.445	0.9836	0.208	0.9982	0.3723	0.9815	51.78
F12	0.7272	5.832	0.9715	0.199	0.9600	0.2639	0.9260	43.15

E) Fourier Transform Infrared (FTIR) spectroscopic studies:

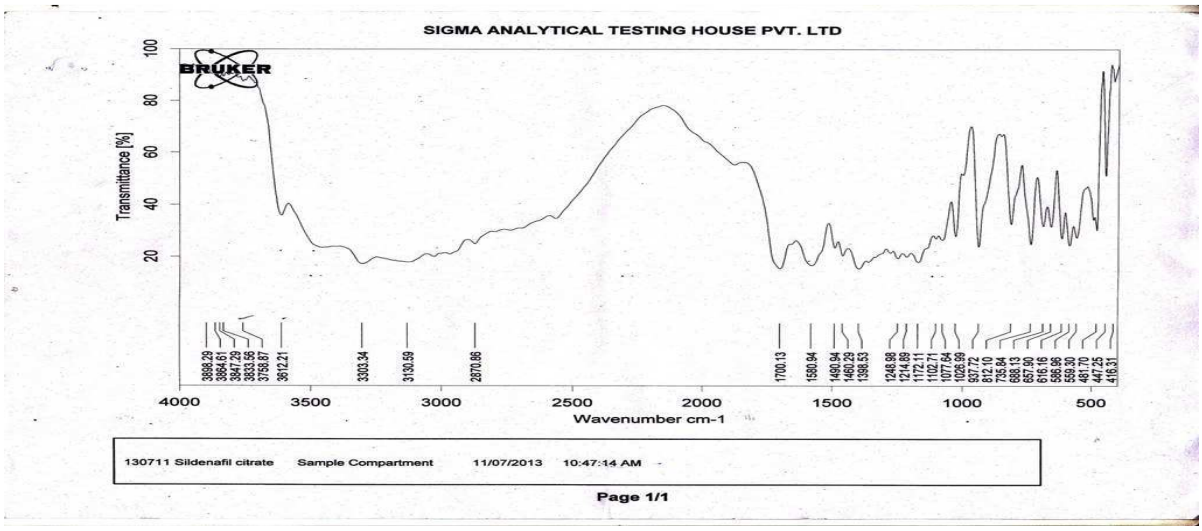

Fig no.3 FTIR of Pure drug.

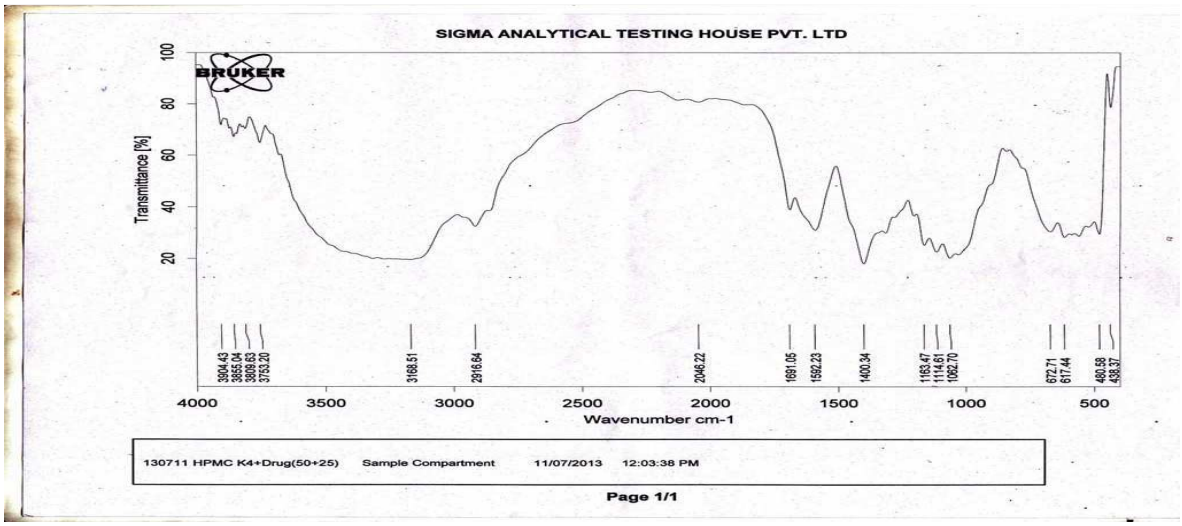

Fig no.4 FTIR of Optimized formulation.

Conclusion

Bilayered sustained Release matrix system is one of the important method of providing sustained drug delivery in a predetermined manner. Among all the formulations, the formulation F10 prepared with Hydroxy Propyl Methyl

Cellulose (HPMC K4M) showed the best result based on its highest f2 value (67.73).This dosage form can be considered suitable for further *in vivo* studies which can be extrapolated for a new delivery system.

References

1. Notari, R., Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York, 1980, p152- 54.
2. Lechman, L., Liberman, H.A., Kanig, J.L., In., The Theory and Practice of Pharmacy,3rd Ed., Varghese Publishing House, Bombay, 1987, p 430-453.
3. Formulation and invitro evaluation of matrix tablet containing sildenafil citrate.
4. Timmermans J, Moes AJ. Factors controlling the buoyancy and gastric retention capabilitiesof floating matrix capsules: New data for reconsidering the controversy. J. Pharm. Sci. 1994; 83 : 18
5. Clarke GM, Newton JM, Short MD. Comparative gastrointestinal transit of pellet systems of varying density. Int. J. Pharm. 1995; 114 : 1-11.
6. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharma Sci**.** 1961; 50; 874 – 875.
7. Hixson AW. Crowell JH. Dependence of reaction velocity upon surface and agitation. IndEng Chem. 1931 ; 23; 923 – 931.
8. Korsemeyer R, Gurny R, Peppas N. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15; 25-35.
9. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv.1985; 60; 110 – 111.
10. Deshpande et al .Bilayer tablets an emerging trend a review..*IJPSR*, 2011; Vol.2(10): page no:2534-2544.
11. KottaKranthi Kumar et al. Design , development and characterization of sustained release of metformin and gliclazidebilayered tablets. *International Journal of Biopharmaceutics.* 2010; vol1(2): Page no:67-71.
12. Mahajan*et al*., (2011) was conducted to develop formulation of valsartan using HPMC alone and in combination with ethyl cellulose as the matrix material in different proportion by wet granulation method.
13. DoddayyaHiremath evaluated controlled release bilayer tablet of Losartan Potassium, *International journal of pharmaceutical research,* (2010);34-39.

14. AshishAPahadeet al., Formulation and development of a bilayer sustained released tablets of IsosorbideMononitrate, Internatonal Journal of pharma and Biosciences, 2010; 305-314.
15. Ramesh et al.,Formulation and evaluation of the bi-layered sustained release matrix tablets of metformin Hcl and Pioglitazone. American-Eurasian Journal of Scientific Research, 2010; 176-182.
16. Imran Nazir Preparation and INVITRO Dissolution of Glipizide Sustained Release Tablets,Turk journal of pharmaceutical sciences,2009,43-50.
17. Raymond C Rowe., Paul J Sheskey., Marian E Quinn. Handbook of Pharmaceutical Excipients.2009.
18. Hadjiioannou T P, Christian G D, Koupparis M A. *Quantitative Calculations in Pharmaceutical Practice and Research.* VCH Publishers Inc, New York, NY, pp. 1993; 345-348.
19. olton S, Bon C. Pharmaceutical Statistics: *Practical and Clinical Applications.* Marcel Dekker, New York, 2004.
20. Lopes CM, Lobo JMS, Costa P, Pinto JF. Directly compressed mini matrix tablets containing ibuprofen: preparation and evaluation of sustained release. *Drug DevInd Pharm.* 2006; 32:95-106.

Corresponding Author:
KrishnakanthJadhav*,
Email: *krishnakanth.jadhav@gmail.com*