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Preparation & Evaluation of Sildenafil Citrate as Anti Impotence Drug by Fast Dissolving Film Approach

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ABSTRACT: The purpose of the present work was to establish Sildenafil Citrate's rapidly dissolving oral film to resolve the constraints of current routes of administration, to provide urgent intervention and to improve patient compliance. Using different grades of Hydroxy Propyl Methyl Cellulose (HPMC) and various plasticizers such as Polyethylene Glycol (PEG) 400, glycerol, Propylene Glycol (PG) by solvent casting process, rapidly dissolving oral film was developed to boost the bioavailability of the drug. For film thickness, surface pH, folding endurance, weight variation, percent moisture loss, exvivo permeation analysis, tensile strength, percent elongation, uniformity of drug material, in vitro dissolution tests, in vitro disintegration test study, the formulated films were evaluated. The prepared formulations for in vitro dissolution, solution time and their physical-mechanical parameters, mainly tensile strength, were evaluated using experimental design. The optimized formulation (batch F4) containing HPMC E15, propylene glycol, glycerin T-80 showed drug dissolution with adequate taste masking and other physico-mechanical properties appropriate for mouth dissolving film (more than 92 percent within 10 minutes).

KEYWORDS: Fast dissolving oral film; Sildenafil Citrate; Plasticizer; Solvent casting

I. INTRODUCTION

Sexual relationships are some of the most important social and biological relationship in human life. Male impotence also called erectile dysfunction (ED) is a common medical condition that affects the sexual life of millions of men worldwide. Erectile dysfunction is defined as the inability of a man to achieve and maintain an erection sufficient for naturally satisfactory intercourse. Sexual dysfunction is a serious medical and social symptom that occurs in 10-52% of men and 25-63% of women (Porst-2004). The available drugs and treatments have limited efficacy, unpleasant side effects & contraindications in certain disease conditions. Sildenafil Citrate (Viagra) is a successful drug that modifies the heamodynamics in the penis [1,2].

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity [3]. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. (FDF) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery [4-9] capitalized on the opportunity to transition this technology to FDF formats. Today, FDF are a proven & accepted technology for the systemic delivery of APIs for over-the-counter FDF medications & are in the early- to mid-development stages for prescription drugs.

Sildenafil Citrate is a successful drug that modifies the heamo dynamics in the penis [10-12]. The intention of the existing studies became to expand speedy dissolving movie of sildenafil citrate which now no longer best gives fast onset however additionally gives precise product differentiation from different advertised product inclusive of movie covered capsules, bubbling capsules, chewable capsules etc. The oral route of sildenafil citrate administration is the most common and convenient for patient use. sildenafil citrate produce 40% biological availability. Mouth throght it goes to systemic circulation without passing through first pass metabolism. An ideal quick dispersing/

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dissolving delivery system should have the following properties: high stability, transportability, ease of handling and administration, no special packaging material and/or processing requirements, no water necessary for application and a pleasant taste [13]. Therefore, a need exists for a quick dispersing/dissolving delivery system with the aforementioned capabilities for use within the pediatric and geriatric populations. The mouth dissolving film of sildenafil citrate (SC) overcomes the shortfalls of conventional quick dispersing/ dissolving intraoral tablets. Tensile strength and % elongation at break study was carried out at Gujarat Print Pvt Ltd, Mahesana. Sildenafil citrate film was produce by solvent casting method.

II. EXPERIMENTATION

Materials: Sildenafil citrate (SC) was procured from mercury Lab pvt Ltd, Baroda. Other materials like HPMC (E5, E6, E15 E55) povidon, pactin, Carrageenan, (EC) ethyl cellulose, poly caprolactum (PCL), dextran-T, guargum, xanthan gum, carboxy methyl cellulose (CMC), micro crystalline cellulose (MCC), glycerol (G-ol), citric acid(CA) Sodium saccharin, Citric acid, PEG-400 (P-400), Sorbitol, Tween-80 (T-80), Sorbitol (S-ol) etc. used were of pharmacological grade.

Preparation Of Fast Dissolving Film: Here 33 formulations for FDF of SC were prepared using film forming polymers [HPMC-(E5,6,15,55), povidon, pectin, carrageenan, EC, PCL, dextran-T, guargum, xanthan gum, CMC, MCC), plasticizer (PEG 400, Glycerol), other ingredients: sweetener (Sodium Saccharin), flavourant (piper oil) saliva stimulating agent (CA) and 70% aqueous solution of sorbitol. The film forming polymer was dissolved in ethanol (EtOH) and other ingredients were dissolved in methanol (MeOH). Pour the ingredients solution drop by drop in previously prepared film forming solution with constant stirring to form clear solution. The solution was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass Petri dish having area of 76 cm^2 and was dried at room temperature. The Petri dishes were put on the levelled surface during drying to avoid variation in the thickness. The film took approximately 24 hours to dry at room temperature. The dried film was carefully removed from the mould and was cut into size required for testing. All batches contain 100 mg of sildenafil citrate which is equivalent to 8 mg SC per film of 2×2 cm^2 area for preparation (FDF) [14].

Different polymer based comparative trial (first batch): sixteen formulations (P1-16) were prepared by using glycerol and PEG 400 as a plasticizer in a fixed quantity with different polymer (Table-1).

Compatibility of polymer & plasticizer with SC (Second batch): seven formulations (SC1-7) of FDF were prepared using fixed quantity of ingredients & different concentration of SC (Table-2).

Optimisation of concentration of selected polymer: Third batch, twelve formulations (F1-12) of FDF were prepared using fixed quantity of ingredients & different concentration of selected polymer (Table-3).

Evaluation of Fast Dissolving Film:

Fast dissolving film should be stiff, flat and should not curl on the edges. The fast dissolving film strip must be robust enough to be removed from the unit-dose packaging and to be handled by the consumer without breaking. The film must also dissolve readily in order to deliver the active agent rapidly when placed in the oral cavity. Mechanical property of fast dissolving film plays an important role in deciding the formulations [15-16].

Physical parameters: Appearance: Physical appearance may be transparent or opaque involves number of attributes such as width, and unique identification marking.

Separatability: The ease of film separation from the separability and in vitro dissolving time were considered for the selection of best film from various batches prepared as well as for the selection of the polymer for further studies. The coding given below,

Separability	Code
Good	++
Moderate	+
Poor	-

Thickness: The thickness of each sample was measured using a micrometre at five locations i.e. centre and four corners.

Percentage Elongations at break: Percentage elongation at break (%E) is calculated by dividing the extension at the moment of rupture of the specimen by the initial gage length of the specimen and multiplying by 100.

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Table-1: Different polymer based comparative trials batch

Batch code	Weight in gm					Volume in ml			
	Polymer (0.7 gm)	CA	SC	P-400	S-ol	T-80	G-ol	EtOH	MeOH
P1	HPMC E5	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P2	HPMC E6	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P3	HPMCE15	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P4	HPMCE55	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P5	Povidone	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P6	CAB	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P7	Guargum	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P8	Xanthan gum	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P9	Gelatin	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P10	Dextran T	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P11	Caraginannan	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P12	Pactin	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P13	CMC	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P14	MCC	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P15	PCL	0.01	0.1	0.06	0.2	Qs	0.06	7	4
P16	EC	0.01	0.1	0.06	0.2	Qs	0.06	7	4

Table-2. Different Sildenafil Citrate Content

Weight in gram			Volume in ml					
Batch code	SC	HPMCE5	P- 400	G-ol	S-ol	T 80	EtOH	MeOH
SC 1	0.5	0.7	0.06	0.06	0.2	Qs	7	4
SC 2	0.4	0.7	0.06	0.06	0.2	Qs	7	4
SC 3	0.3	0.7	0.06	0.06	0.2	Qs	7	4
SC 4	0.2	0.7	0.06	0.06	0.2	Qs	7	4
SC 5	0.15	0.7	0.06	0.06	0.2	Qs	7	4
SC 6	0.125	0.7	0.06	0.06	0.2	Qs	7	4
SC 7	0.1	0.7	0.06	0.06	0.2	Qs	7	4

Table-3. HPMC E5/E6/E15/E55 Polymer containing film

Weight in gram				Volume in ml						
Polymer (%)	SC	CA	SS	P- 400	G-ol	S-ol	T80	P-oil	EtoH	MeoH
5 %	0.1	0.01	0.01	0.06	0.06	0.2	Qs	0.05	7	4
7.5 %	0.1	0.01	0.01	0.06	0.06	0.2	Qs	0.05	7	4
10%	0.1	0.01	0.01	0.06	0.06	0.2	Qs	0.05	7	4

HPMC E5/E6/E15/E55 Polymer 5%w/w is signed respectively as F1 /F4/F7/F10. HPMC E5/E6/E15/E55 Polymer 7.5%w/w is signed respectively as F2/F5/F8/F11. HPMC E5/E6/E15/E55 Polymer 10%w/w is signed respectively as F3/F6/F9/F12.

*All batches contain 100 mg of sildenafil citrate

Folding endurance: Folding endurance was determined by repeatedly folding the film at the same place till it break. The numbers of times the film can be folded at the same place without breaking give the value of folding endurance [17].

Test mask: These formulations are for adults person and remain few seconds in mouth cavity so the taste intensity should be justified. The taste acceptability was measured by a taste panel. Each formulation was given to a taste panel expert

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(healthy human volunteers) and was held in the mouth for 10-15 seconds, then spit it out and the overall palatability level was recorded as A,B,C and D grade as mentioned in Table-4.

Table -4. Overall palatability grades for formulation

Grade	Overall palatability
A	Very good
B	Good
C	Average
D	Poor

Morphology study: Morphological study providing information regarding surface study of FDF [18]. Morphology study of FDF was carried out by Compound microscope (model RH-70, Unilab, Bangalore)

Measurement of in vitro disintegration/ dissolution: In vitro Disintegration study: The in vitro dissolving time was measured (n=3) for film of each batch in 20 ml of simulated saliva at pH 6.8 in glass Petridis. Film sample (2 cm x 2 cm) was placed in 20 ml of simulated saliva. The medium was kept mildly agitated using a magnetic stirrer. The time for complete dissolution of the film was recorded as dissolving time. The average of three measurements was taken into consideration.

In vitro dissolution: The dissolution study was carried out using USP paddle apparatus, at 370C ± 0.50C using 300 ml of simulated saliva at pH 6.8 as dissolution medium. The agitation rate of paddle was 50 rpm. An equal volume of the fresh dissolution media, maintained at the same temperature was added after withdrawing the sample to maintain the volume. Then the solution samples were analysed in UV-VIS double beam spectrophotometer (Systronics UV-VIS spectrophotometer 118) while replacing the dissolution media as a blank.

Stability testing: Films of optimized batches were subjected to stability study. Each film was wrapped in a butter paper and placed in plastic zip bag. Films were exposed to 75% remain in humidity, 400 C temperature and ordinary room temperature. The study was carried out for 10 days. The films were evaluated initially and every 10 days for their physical characteristics, in vitro Disintegration, drug content uniformity and folding endurance.

Drug excipients compatibility study: FTIR Study: The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch were measured using Fourier Transform Infrared Spectrophotometer. The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400 cm-1.

III. RESULT AND DISCUSSION

Evaluation of Fast Dissolving Film:

The visual identity overall elegance consumers acceptability, control or uniformity monitoring and trouble face manufacturing and reflecting of the general appearance of a FDF. The control or physical appearance of FDF involve 5ml measurement of a number of attributes such as thickness, shapes, presence or absence of an odour, taste, visual appearance colour, consistency and identification marking.

Preliminary studies were carried out to select a suitable polymer system and to obtain a good polymer plasticizer system, which is capable of producing films of desirable mechanical property and dissolution characteristics. Results (Table-5, 6) were shows that formulations P1-4 produced good film as compare to others. All films as whole unit were easily peel able from glass Petridis without breaking film, so separability from Petridis is also not issue in all film formulation those prepared from HPMC. Physical appearances (Figure-1) provided by these films gives appreciable result then others. All films prepared with HPMC had very nice clarity and transparency, without any grittiness.

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Figure-1.: The Photograph of 2 x2 cm2 FDF

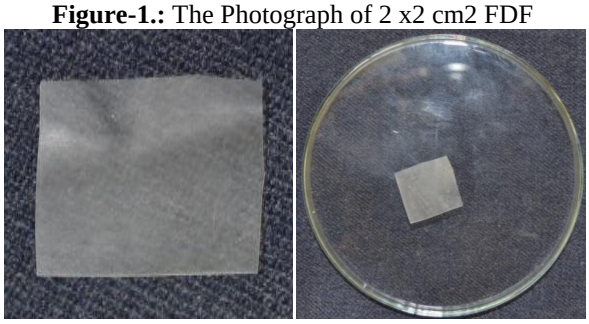

Table-5. Compatibility of different polymers with other ingredients

Formulation ID	Colour	Transparency	Nature	Film Produce
P1-4	Colourless	Transparent	Flexible, Soft	Good
P5	Buff	Opaque	Sticky	Sticky
P6	White	Opaque	Hard	Very Fragile
P7-15	White	Opaque	Hard	Poor
P16	White	Opaque	Hard	Very Fragile

Table-6. Compatibility of HPMC E5 with different SC content:

Formulation ID	Colour	Transparency	Nature	Film Produce
SC 1-5	White	Gritty	Remains powder	Poor
SC 6	Buff white	Opaque	Brittle	Very Fragile
SC 7	Colourless	Transparent	Flexible, Soft	Good

Table-7. Different Batch wise (FDF) Production

Formulation ID	Colour	Transparency	Nature	Film Produce
SC 1-5	White	Gritty	Remains powder	Poor
SC 6	Buff white	Opaque & Gritty	Brittle and hard	Very Fragile
SC 7	Colourless	Transparent	Flexible, Soft	Good

Results (Table-7) shows that the formulation SC7 was superior as compare to others. This indicates that 100mg SC content is compatible with HPMC polymer and other ingredients. Good film forming polymer of HPMC (E5,E6,E15,E55) in concentration 5, 7.5, 10 % with 2% concentration of plasticizer (glycerol and PEG 400) give good result (Table-8) in terms of mechanical properties (for example, tensile strength, folding endurance and % elongation Table-9) as well as disintegration and dissolution characteristics. All films prepared with HPMC had very nice celerity and transparency, without any grittiness. They differed only in case of in vitro dissolving criteria, so according to our aim to achieve disintegration within 2 minute. As the amount of HPMC increased thickness increased and that results into higher disintegration time so optimum thickness that is a key parameter to set fast disintegration was properly justified by optimizing HPMC polymer concentration.

Thickness: As results shown in the table are various parameters like thickness, in vitro DT Time as well as content uniformity was checked. Seeing the data of thickness value of prepared film of nine batches, as the concentration of polymer HPMC increase from 5%-10%, increase in the thickness of prepared film (Table 3.5). So there is direct linear relationship observed between thickness of film and amount of HPMC LV present. There was no such relationship observed with amount of glycerine and thickness of film. So by optimising the amount of polymer we can control the thickness and that will further be optimised in-vitro DT time indirectly.

Palatability: All the formulations were tasted in healthy human volunteer and asked to be categorized, in A, B and C grade as decided in experimental methodology section of it. All formulations got A and B grade which indicate that all formulations have acceptable palatability as

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well as no more problem of bitter taste of Sc, so all the formulations were not palatable (Table 3.5). Results shows that various grade (E5, 6, 15, 55) of HPMC gives a good result in terms of mechanical properties. Approximate 5% w/v concentrations of film former HPMC E6 requires to achieve desired results (Formulation F4).

Morphology:

This was supported by microscopic study results of the film, there were no any transverse scratches on the film (Figure-2). There were slight whitish small particle like image which may be drug or any another excipients that was recrystallised in minute amount but that was not seen by human eyes as such, so no more problem of patient incompliance.

Table-8. Different Batch Wise (FDF) Production

Formulation ID	Polymer %	Transparency	Nature	Film produce
F1	5	Transparent	Sticky, soft film	Good
F2	7.5	Opaque	Flexible	Good
F3	10	Opaque	Flexible	Good
F4	5	Transparent	Flexible	Best
F5	7.5	Transparent	Flexible	Better
F6	10	Transparent	More flexible	Good
F7	5	Transparent	Flexible	Better
F8	7.5	Transparent	Flexible	Good
F9	10	Opaque with air bubble	More flexible	Good
F10	5	Transparent	Flexible	Better
F11	7.5	Transparent	More flexible	Good
F12	10	Opaque	Most flexible	Good

Table-9. Results of mechanical properties

ID	Thickness	Elongation	Tensile	Folding	Palatability	Separability
F1	130.17±2.32	50.15	3.22	15	A	+++
F2	140.67±2.94	69.32	3.75	28	B	+++
F3	210.3.3±1.97	85.39	4.10	33	B	++
F4	80.83±3.31	88.41	4.27	43	A	+++
F5	100.00±3.74	96.29	4.89	>50	B	++
F6	228.83±4.31	99.71	5.08	>50	C	+
F7	100.12±2.88	68.10	5.30	48	A	+++
F8	110.17±3.54	73.62	6.36	>50	B	++
F9	180.13±1.11	92.13	6.42	>50	C	+

Figure-2: The microscopic photomicrograph of optimized SC film (batch F4).

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Measurement of In Vitro Disintegration, Dissolution And Drug Content:

Spectroscopic estimation of Sildenafil citrate: Preparation of standard curve of SC in Phosphate buffer saline solution (PH 6.8): SC (100mg) was discovered in PBS Solution and volume is made up to 100ml in volumetric flask. And from this solution 1ml, 1.5ml, 2.0ml & 2.5ml in different test tubes are withdrawn and volume made up to 10ml with PBS solution. Absorbance of each solution was measured of 363nm using UV Spectrophotometer (Systronics UV-VIS double beam spectrophotometer 118). PBS solution was used as a reference standard.

- The standard curve was generated for entire range from 1 to 2.5 □g/ml.
- The experiment was performed in triplicate & based an average absorbance.
- The result of standard curve preparation is as shown in Table 10 & Figure - 3.

In vitro disintegration and dissolution: In vitro disintegration study (Table-11) is main key parameter to determine the amount of drug release in shorter period of time and simultaneously faster onset of action. Results shown in below table indicate that as the amount of polymer increase, in vitro disintegration study time increased proportionally since thickness of film increased as shown below.

Content uniformity: Content uniformity is also important consideration in administering the precise dose in patient and thus content uniformity were evaluated for all factorial design batches and results are shown in table .Content uniformity is solely dependent on the manufacturing process. Results indicate that all batches had content uniformity more than 90% which was non problematic in case of sildenafil citrateate. There were no significant changes observed for content uniformity with respect to polymer and plasticizer concentration in these experiments. HPMC E55 polymer containing films are not shown disintegration & dissolution.

Drug realise study: Have a result basis dissolution profile various formulation sildenafil citrate was almost completely release from all the formulation within 5 minutes. Sildenafil citrate from all FDF studied in buffer medium PH 6.8 release data given below. Various drug released from FDF with different polymer & different concentration for different formulation.

Table-10. UV Absorbance of standard solution of SC in PBS Solution (pH:6.8):

Concentration (□g/ml)	Absorbance			Absorbance mean
	1	2	3	
5	0.13	0.13	0.14	0.13
10	0.26	0.29	0.25	0.27
15	0.36	0.41	0.38	0.39
20	0.58	0.54	0.51	0.55
25	0.69	0.65	0.66	0.67
30	0.79	0.84	0.78	0.81

Figure -3 spectroscopic evaluation with absorbance vs. concentration:

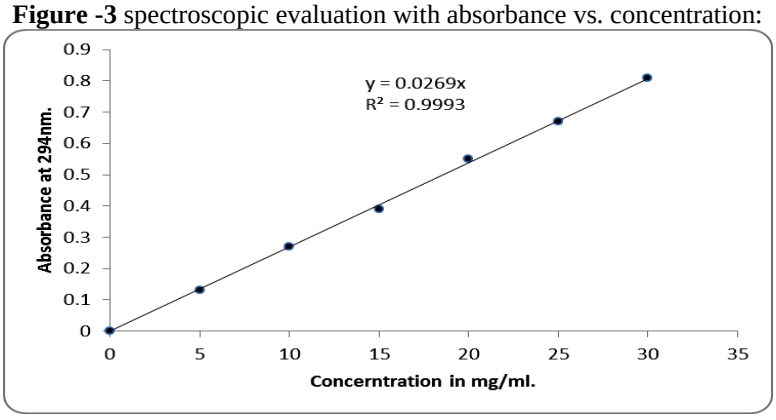

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Table-11: In vitro disintegration and drug content

Batch code	In vitro D.T (Sec)	% Drug Content Realize
F1	55.23	96
F2	103.83	77
F3	175.00	61
F4	62.17	92
F5	125.33	73
F6	190.19	52
F7	90.83	84
F8	160.16	59
F9	258.12	33

Drug Excipients Compatibility Study:

Furrier transfer infrared (FT-IR) Study: FTIR spectroscopy was used as mean of studying drug excipients compatibility. The FTIR of pure drug and optimized batch formulations (F1-12) were scanned over a wave number range of 4000 to 400 cm^{-1} (Figure - 4 & 5). In IR Spectrum of pure sildenafil citrate showed the presence of peak at 3458 cm^{-1} (hydrogen bonded coupled with stretching vibrations NH starching of NH_2 moiety), 3298 cm^{-1} (OH starching), ~1650, ~1590 cm^{-1} (C=N stretching), ~1690 cm^{-1} (coupled vibrations of C=O and C=N stretching and NH_2 bending arising from the amino acids/ amides), ~1710 cm^{-1} (C=O stretching in unionized carboxylic moiety of citrate) group were characteristic of pure drug and all of them remain unaltered in IR spectrum of formulations, which indicate no drug excipients interactions.

Stability Study: Films of optimized batches F4 was subjected to stability study for 10 days. Film was exposed to 75% RH & 40°C temperature and ordinary room temperature for initially and every 10 days for their physical characteristics, in vitro Disintegration, drug content uniformity and folding endurance. Stability (Table-12) study suggested that the optimized batch formulation F4 was stable at room temperature condition. Results suggest that with increase in temperature the amount of moisture in the film gets decreased, which in turn into hard, brittle, increased disintegration and may diminished the film forming properties of HPMC.

IV. CONCLUSION

The fast dissolving sublingual films of sildenafil citrate were obtained by the solvent casting method. It showed acceptable mechanical properties and satisfactory drug release after 1 minute for optimized batch formulations (F1-9). The prepared film was transparent with smooth surface without any drug excipients interaction. The multiple regression analysis of the results led to such equations that describe adequately the influence of the selected variables concentration of HPMC E6 and concentration of glycerol & PEG-400 on the responses under study. The desirability function led to the optimum values of the factors at which the produced film showed fast drug release and suitable mechanical properties.

The film F4 stored under normal room temperature for 10 days did not show any changes with respect to content uniformity, physical appearance, in vitro disintegration and folding endurance. While the same formulation F4 was not stable at accelerate condition (75% RH and 400C). Further there is a need to cheque the stability for long period of time (2 – 3 years) for their suitability.

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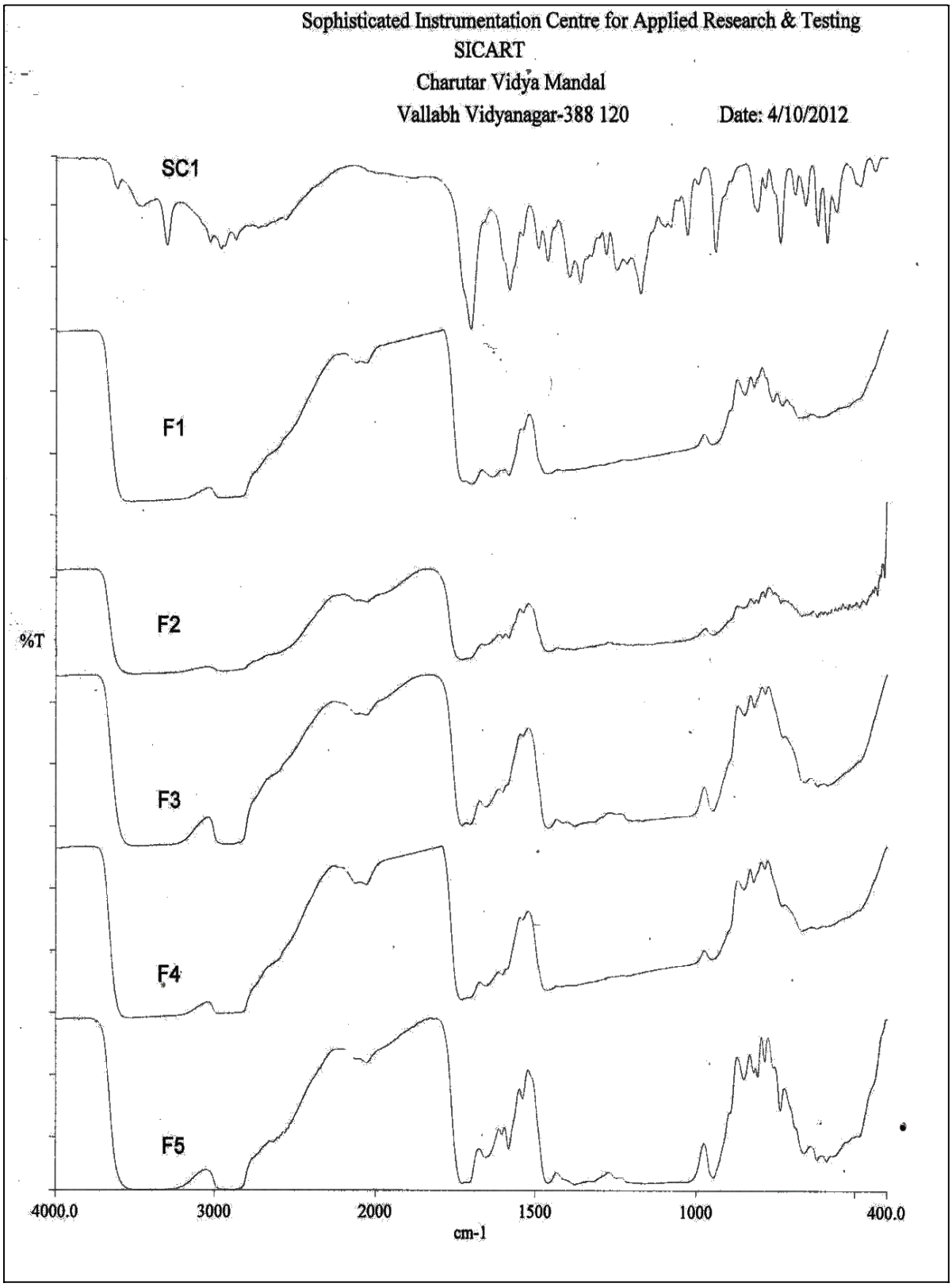

Figure-4. FTIR of Sildenafil citrate & F1-5

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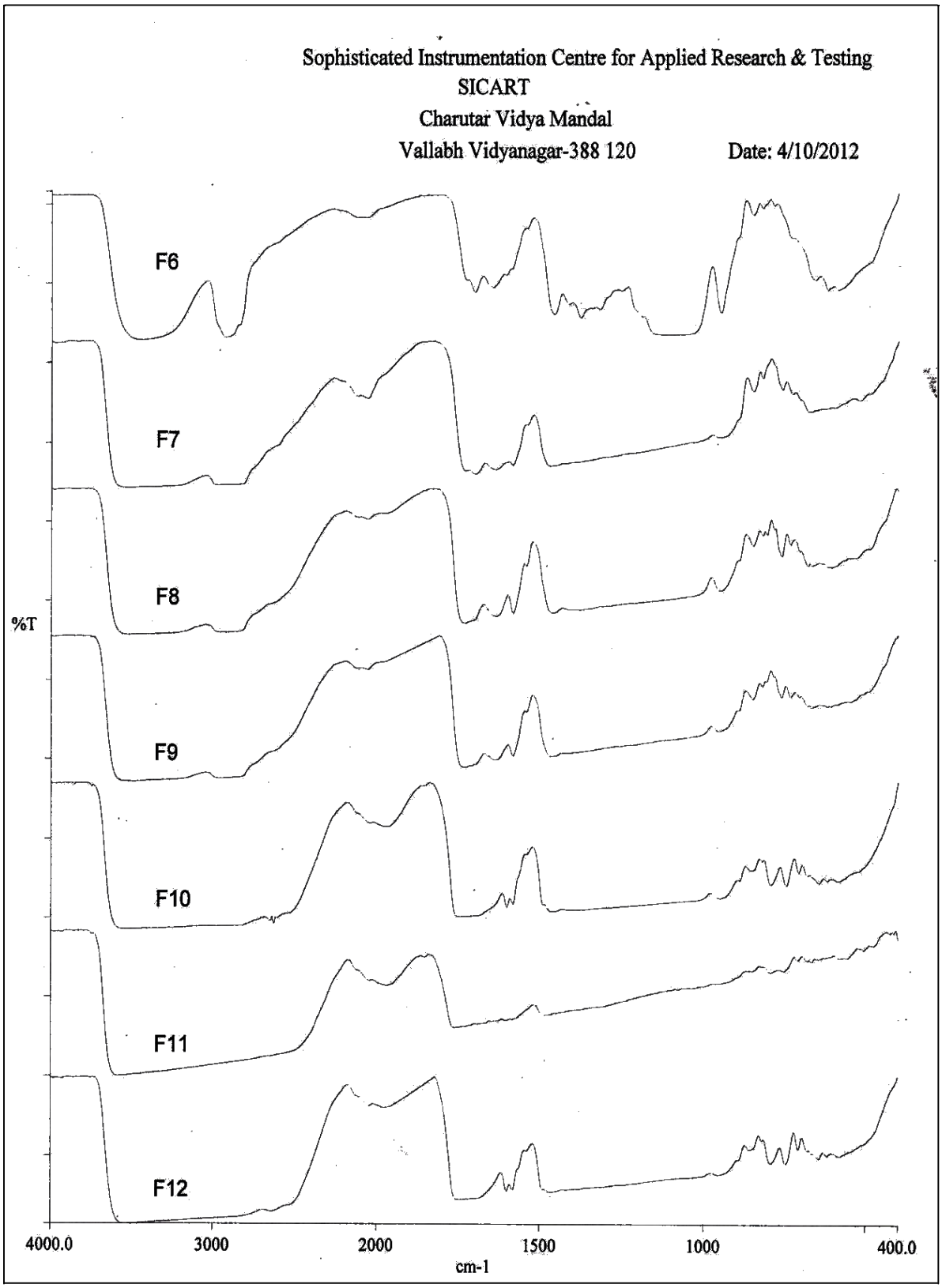

Figure-5. FTIR of F6-12

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Table-12: Results of stability data for F4 batch

Stability condition	Sampling time (Days)	Folding endurance	In vitro disintegration (seconds)	Visual appearance	Drug content uniformity
Room condition	0	43	62.14±0.12	Clear homogeneous film	94.30±4.37
	5	40	65.45±0.45		93.15±3.88
	10	39	64.11±0.55		94.94±4.78
40°C & 75% RH	0	43	62.14±0.12	Clear homogeneous film	94.30±2.98
	5	30	67.14±0.34		93.67±3.67
	10	19	72.12±0.23	Slight hazy film	92.17±2.88

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