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FORMULATION, DEVELOPMENT AND IN VITRO EVALUATION OF SILDENAFIL CITRATE LIGNOCAINE HCl GEL

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Abstract:

The present study was undertaken to formulate, development and in vitro evaluation of Sildenafil Lignocaine gel. Sildenafil citrate is a drug of choice used in the treatment of premature ejaculation disorder. Topical gel has gained more and more importance because the gel based formulations are better percutaneously absorbed than creams and ointment bases. Therefore, topical gel of Sildenafil citrate was prepared using polymer of Carbopol 934 and triethanolamine at different proportions. The study encompasses compatibility studies using FTIR spectra, drug content, viscosity, spreadability, and pH determination. Further the optimized formulation F5 was evaluated by in vitro diffusion study. Optimized formulation batch F5 subjected to stability as well as in vitro study. The preliminary compatibility studies conducted revealed that there was no interaction between Sildenafil citrate and excipients. In vitro drug release study was carried out with Franz diffusion cell using egg membrane in pH 7.4 phosphate buffers as diffusion medium. Formulation batch F5 containing Carbopol 934 and triethanolamine showed 99.09 % drug release at 60 min and 5.55 g.cm /sec spreadability. Result showed that formulation batch F5 showed better drug release at one h. Formulation batch F5 was used further for stability and ex vivo study. Stability studies conducted under accelerated condition were shown satisfactory results. It was concluded that Carbopol gel containing Sildenafil citrate showed good consistency, spreadability, homogeneity and stability. So, topical gel had wider prospect for topical preparations.

Keywords: *Sildenafil citrate, Carbopol 934, Triethanolamine, Topical gel of Sildenafil citrate.*

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INTRODUCTION:

Premature ejaculation is one of the most common forms of sexual dysfunction and is thought to affect up to 30 % of men. Both the term "premature ejaculation" (PE) and the term "rapid ejaculation" (RE) are used to describe this condition. The WHO second International Consultation on Sexual Dysfunction proposed a multivariate definition for PE: "Premature ejaculation is persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has little or no voluntary control which causes the sufferer and/or his partner bother or distress." [1,2].

Topical gel preparations are intended for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. Gels are typically formed from a liquid phase that has been thickened with other ingredients. The continuous liquid phase allows free diffusion of molecules through the polymers scaffold and hence release might be equivalent to that from a simple solution. Topical gel reduces the adverse drug reaction associated with oral formulations. Topical application of gels at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compare to creams and ointments [3,4].

Topical delivery is an attractive route for local and systemic treatment. The delivery of drugs onto the skin is recognized as an effective means of therapy for local dermatologic diseases. It can penetrate deeper into skin and hence give better absorption[5].

Desired physicochemical properties of drug which required for formulation of topical hydrogels are

i) Drug should have a molecular weight of less than 500 Daltons.

ii) Drug must have adequate hydrophilicity.

iii) A saturated aqueous solution of the drug should have a pH value between 5 and 9.

iv) Drug highly acidic or alkaline in solution is not suitable for topical delivery[6].

MATERIALS AND METHODS:

Sildenafil Citrate were kindly supplied by Ajanta Pharma (Aurangabad, India), Lignocaine hydrochloride was supplied by Manan Healthcare (Banglore, India). All the products and materials used in this study comply with the pharmaceutical and analytical standards, respectively.

All the research work was carried out at KBHSS Trust Institute of pharmacy, Malegaon, Maharashtra during year 2017-2018.

1. Preformulation Studies: Preformulation testing is the first step in the rational development of dosage forms of drugs. It involves the application of biopharmaceutical principles to the physicochemical parameters of a drug with the goal of designing an optimum drug delivery system that is stable, bioavailable and can be mass-produced.

Preformulation testing is defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

The goals of Preformulation studies are:

- To establish the necessary physiochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish it's compatibility with different excipients.

Hence, Preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies.[7]

2. U. V. Spectrum: The UV spectrum of sildenafil citrate in 0.1N HCl solution was scanned at 400-200 nm.

a) **Determination of λmax:**

UV spectrum of sildenafil citrate was carried out in 0.1N HCl solution. Sildenafil citrate (100mg) was accurately weighed and transferred into the 100 ml volumetric flask . It was dissolved in 0.01 M HCl and volume wasmade up to the mark with 0.1N HCl to get a 1000 µg/ml solution. From this 10 ml was pipette out and then diluted up to 100 ml with 0.01M

HCl. From that solution again 10 ml pipetted out and diluted up to 100 ml in volumetric flask with 0.01M HCl to get a stock solution of 10 µg/ml. UV scanning was done for drug solution from 200-400 nm in 0.01M HCl as a blank using Lab India double beam UV/VIS spectrophotometer. Wavelength for maximum absorbance was recorded.

b) Calibration Curve by UV Spectroscopy:

Preparation of Standard Curve of Sildenafil Citrate:

From the stock solution 2,4,6,8,10 and 12 ml were transferred to 100 ml volumetric flask and diluted with the 0.1N HCl up to the mark to obtain Sildenafil citrate concentration of 2,4,6,8,10 and 12 µg/ml respectively. Absorbance of each solution was measured at **λmax**. Using this concentration absorbance data. Beer Lambert graph was plotted.

3. Infra-Red Fourier Transform Spectroscopy:

FTIR spectrum of sildenafil citrate was obtained using KBr pellet technique. Scanned from 4000cm-1 to 400cm-1 in FTIR spectrophotometer. The obtained spectra was interpreted with standard spectra for identification of pure drug.[8]

3.1. Drug-Excipient Compatibility Studies:

Fourier Transform Infrared Spectroscopy (FTIR): IR spectroscopy was used to determine the molecular interaction between polymer and drugs. All physical mixture and drugs sample were mixed with dried KBr in ratio 1:1. Then small fraction of mixtures was compressed on automatic IR press at pressure 10 tones to from transparent pellet. Then the IR spectrum of pellets was taken on FTIR spectrophotometer. The identified peaks were compared with the principle peaks of reported IR spectrum of sildenafil citrate and the sample was authenticated.[8]

The infrared spectrum of physical mixture of sildenafil citrate: Sildenafil citrate, Sildenafil citrate : Lignocaine hydrochloride (1:1), Sildenafil Citrate : Carbopol : Lignocaine hydrochloride : Methyl paraben : Propyl paraben : Sodium meta bisulphate (1:1:1:1:1:1) mixtures were recorded by potassium bromide dispersion technique in which mixture of polymer : sildenafil citrate and potassium bromide was placed in sample holder and an infrared spectrum was recorded using FTIR spectrophotometer (Jasco-4100, Japan). The identified peaks were compared with the principle peaks of reported IR spectrum of sildenafil citrate and respective polymers.[8]

4. Determination of Thermal Behaviour by Differential Scanning Calorimeter (DSC):

Samples were accurately weighed and encapsulated in flat bottomed Aluminium pans with crimped-on lids. The DSC patterns were obtained with a DSC-60ws differential scanning calorimeter. The measurement from 30 to 3000C were obtained at a scanning speed of 10º c/min under a nitrogen stream at a flow rate of 40 ml/min.[9]

5. Formulation and Development:

The gel consisted of Sildenafil citrate used as a erectile dysfuntion, Lignocaine hydrochloride and gelling agent such as Carbopol 934, Propylene glycol use as a solubilizing agent, Triethanolamine use as a PH adjustment, Sodium metabisulfite, Propylparaben, Methylparaben used as a preservative, Distilled water is used as a vehicle.

Table.No.1. Formulation of Sildenafil Citrate Lignocaine Gel:

Sr.No.	Name of Ingredients	Number of Formulation (Qty in %w/w)				
		F1	F2	F3	F4	F5
1	Sildenafil Citrate	2.9	2.9	2.9	2.9	2.9
2	Lignocaine HCl	3	3	3	3	3
3	Carbopol 934	0.5	0.8	1.0	1.2	1.5
4	Propylene glycol	3.0	3.0	3.0	3.0	3.0
5	Triethanolamine	0.2	0.4	0.7	0.9	1.1
6	Sodium meta bisulphate	0.05	0.05	0.05	0.05	0.05
7	Methyl Paraben	0.05	0.05	0.05	0.05	0.05
8	Propyl Paraben	0.05	0.05	0.05	0.05	0.05
9	Perfume	1.0	1.0	1.0	1.0	1.0
10	Distilled Water	89.25	88.75	88.25	87.85	87.35

5.1. Procedure for Formulation of Sildenafil Citrate Lignocaine Gel:

1.5 gm of Carbopol-934 was dispersed in 26ml of distilled water kept the beaker aside to swell the Carbopol-934 for half an hour and then stirring should be done to mix the Carbopol-934 to form gel. Take 26ml of distilled water and require quantity of methyl paraben, propyl paraben, sodium metabisulfite and Lignocaine hydrochloride were dissolved. Further require quantity of Sildenafil citrate was added in the propylene glycol and mix to the above mixture. Finally full mixed ingredients were mixed properly to the Carbopol-934 gel with continuous stirring and triethanolamine. Finally volume made up to 100ml by adding remaining distilled water.

6. Evaluation Parameters of Sildenafil Citrate Lignocaine Gel:

6.1. pH Measurement: The pH of various gel formulations was determined by using digital pH meter.1 g of gel was dissolved in 100 mL freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.[10]

6.2. **Viscosity Measurement:**

Brookfield digital viscometer was used to measure the viscosity of prepared gel formulations. The spindle no. 6 was rotated at 10 rpm. The reading, near to 100 % torque was noted. Samples were measured at 30 ± 1 °C.[11]

6.3. **Spreadability:**

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application. The therapeutic efficacy of a formulation also depends upon its spreading value It was determined by wooden block and glass slide apparatus. Weights of about 2 g were added to the pan and the time was noted for upper slide (movable) to separate Spreadability was then calculated by using the formula:

$$S = \frac{ML}{T}$$

Where,

S = Spreadability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate the slide completely from each other.[12]

6.4. **Homogeneity:**

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.[13]

6.5. Drug content:

A specific quantity (1 g) of developed gel was taken and dissolved in 100mL of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2 h on mechanical shaker in order to get complete solubility of drug. The solution was filtered through 0.45 µm membrane filter and estimated spectrophotometrically at 293 nm using phosphate buffer (pH 7.4) as blank.[14]

6.6. *In-vitro* Drug Diffusion Study:

In-vitro drug release studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell.

The formulated gels were weight up to 1 g and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 RPM; the temperature was maintained at 37 ± 0.50 °C.

The samples of 1 ml were withdrawn at time interval of 10, 20, 30, 40, 50, 60 min. analyzed for drug content spectrophotometrically at 294 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug diffused from gels were plotted against time.[15]

6.7. Mechanism of Drug Release:

Various models were tested for explaining the kinetics of drug release.

To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, HixonCrowell model and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$F = K0.t$$

Where 'F' is the drug release, 'K0' is the release rate constant and 't' is the release time.

The plot of percentage drug release versus time is linear.

First order release rate kinetics:

The release rate date are fitted to the following equation

$$\text{Log}(100 - F) = K t$$

A plot of log % drug release versus time is linear.

Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$F = Kt1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of percentage drug release versus square root of time is linear.

Hixon-Crowell model:

To study the Hixon-Crowell release kinetics, the release rate data were fitted to the following equation,

$$W01/3 - Wt1/3 = k\,t$$

Where, 'Wo' is the original mass/weight of drug, 'Wt' is the mass/weight at 't' time,'k' is Hixon-Crowell constant.

In this model (Wo1/3 - Wt1/3) versus time is linear.

Korsmeyer and Peppas release model:

The release rate data were fitted to the following equation,

$$Mt\ /M\square = k.tn$$

Where, Mt /M□ is the fraction of drug released,

'K' is the release constant,

't' is the release time.

'n' is diffusion exponent, if n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if 0.45 < n < 0.89 then the release is through anomalous diffusion or non-fickian diffusion (swellable and cylinder Matrix).

In this model, a plot of log (Mt/M0) versus log (time) is linear. The dissolution data of Formulation of transdermal gels were fitted to Zero-order, First order, Higuchi, Hixon- Crowell, and KorsmeyerPeppas model to study the kinetics of drug release.[16,17,18]

6.8. *Ex-vivo* drug release study of optimized batch:

Franz diffusion cell was used in study for *ex-vivo* diffusion of drug. The cell consists of two chambers, the donor and the receptor. The donor compartment is open at the top and is exposed to the atmosphere. The receptor compartment is surrounded by a water jacket for maintaining the temperature at 37 °C ± 2 °C and is provided with a sampling port. The diffusion medium was pH 7.4 phosphate buffer, which was stirred with magnetic beads (operated by a magnetic stirrer).

A egg membrane as a membrane was placed between the two chambers. The diffusion media was stirred to prevent the formation of concentrated drug just beneath the membrane. Samples from the receptor compartment were taken at various intervals of time over a period of 1hours and the concentration of the drug was determined by UV Spectrophotometric method using the standard curve. Amount of drug diffused at various time intervals was calculated and plotted against time.

7. Stability Studies:

In any rational design and evaluation of dosage forms for drugs, stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of the drug can be defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

The international conference on Harmonization (ICH) guidelines titled 'stability testing of New Drug substance and product's (Q1A) describes the stability test requirements for drug registration applications in the European union, Japan and the USA.

Stability studies as per ICH guidelines,

Long-Term Testing: 25 °C ± 2 °C / 60 % RH ± 5 % for 12 months.

Accelerated Testing: 40 °C ± 2 °C / 75 % RH ± 5 % for 6 months.

Stability studies were carried out at 40 °C ± 2 °C / 75 ± 5 % RH for the selected formulation for one month.

7.1. Method:

The selected formulation was packaged in air tight plastic container or Aluminium container. They were then stored at 40°C/75% RH, for one month and evaluated for their physical appearance and drug diffused at specific interval of time per ICH guidelines.

RESULTS AND DISCUSSION:

1. U. V. Spectrum:

.□max values of Sildenafil Citrate in 0.1N HCL (Fig.1). While reported λ max of drug is 294nm.

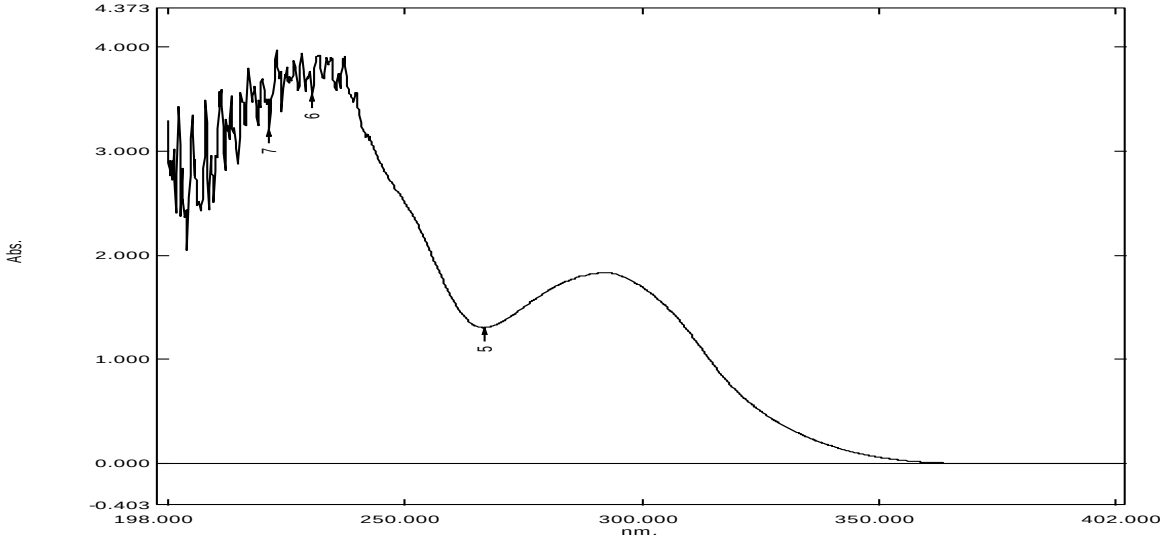

Fig.no.1. U.V. Absorption Spectrum of Sildenafil Citrate in 0.1 N HCL

From the organoleptic properties, melting point and UV Spectrum, the purity of Sildenafil Citrate was identified and it complied with the standards.

1.1. Calibration Curve of Sildenafil Citrate:

From the stock solution 5, 10, 15, 20, 25 and 30 ml were transferred to 100 ml amber colored volumetric flasks and diluted with the 0.1 N HCL, up to the mark to obtained Sildenafil citrate concentration of 2, 4, 6, 8, 10 and 12 µg/ml respectively. Absorbance of each solution was measured at 294 nm. The results are as shown in table no.2. and Fig.no.2.

Table.No.2. Concentration and Absorbance Data of Sildenafil Citrate in 0.1 N HCL

Sr. No.	Concentration in µg/ml	Absorbance			
		I	II	III	Mean
1	0	0	0	0	0
2	2	0.062	0.061	0.061	0.061
3	4	0.122	0.123	0.122	0.122
4	6	0.179	0.188	0.189	0.185
5	8	0.243	0.239	0.241	0.241
6	10	0.300	0.302	0.301	0.301
7	12	0.363	0.370	0.370	0.359
Coefficient of correlation (r2)				0.9998	
Equation of line (y = mx + c)				y = 0.0299x + 0.0017	

*All values are expressed as Mean ±SD, n = 3

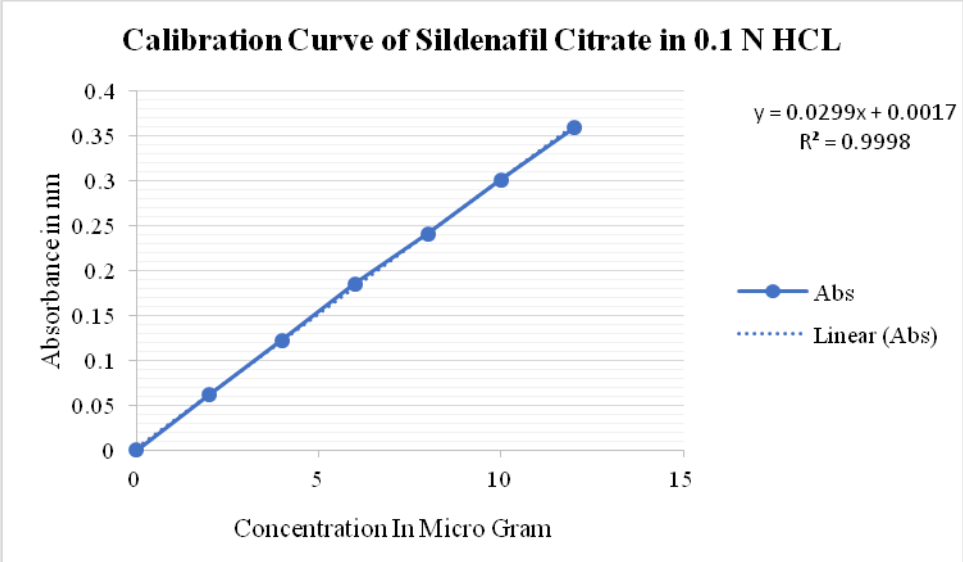

Fig.No.2. Calibration Curve of Sildenafil Citrate in 0.1N HCL

2. I.R. Spectrum:

2.1. IR Spectrum of Sildenafil Citrate:

Table No.3. shows peaks observed at different wave numbers and the functional group associated with these peaks.

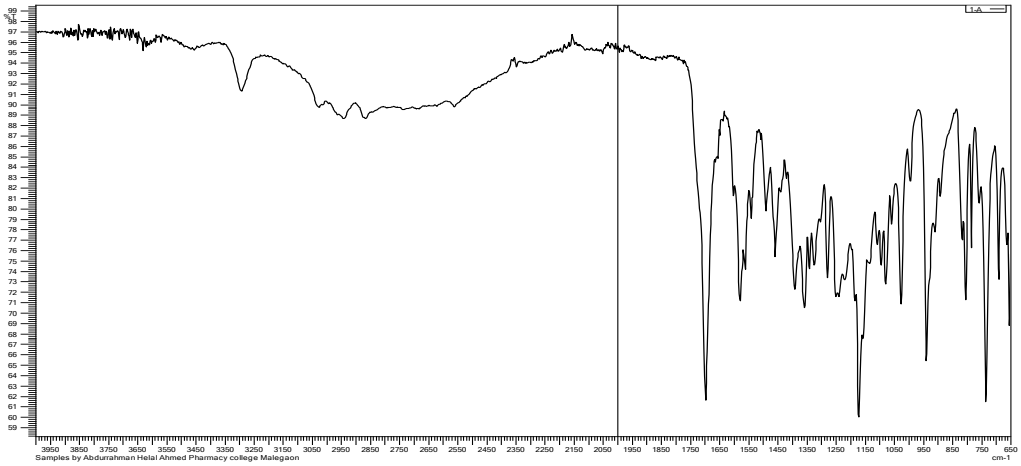

Fig. No.3. IR Spectrum of Sildenafil Citrate

Table.No.3. Characteristics Frequencies in IR Spectrum of Sildenafil Citrate

Functional Group	Characteristics Peak	Observed Peak
O-H stretching	3400-3200 cm-1	3229 cm-1
C-H stretching	3000-2850 cm-1	2941 cm-1
C = N	1690-1640 cm-1	1690 cm-1
N-H	1640-1550 cm-1	1579 cm-1
C-O	1300-1000 cm-1	1170 cm-1
S=O	1375-1300 cm-1	1359 cm-1
C=O	1725 cm-1	1700 cm-1

The IR Spectrum of Sildenafil Citrate reveals the presence of major functional group in the structure of Sildenafil Citrate supporting its identity.

2.2. IR Spectrum of Lignocaine Hydrochloride:

Table No.4. shows peaks observed at different wave numbers and the functional group associated with these peaks.

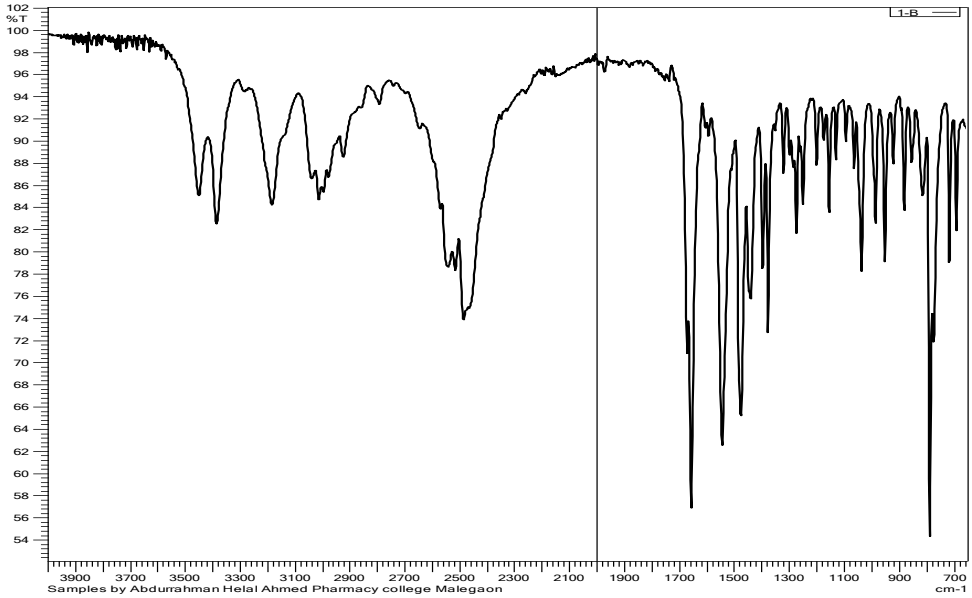

Fig. No.4. IR Spectrum of Lignocaine Hydrochloride

Table. No. 4. Characteristics Frequencies in IR Spectrum of Lignocaine Hydrochloride

Functional Group	Characteristics Peak	Observed Peak
O-H Stretching	3400-3200	3383
C-H Stretching	3000-2850	2922
Amide	1680- 1630	1654
C=N	1690-1640	1654
N-H bending	1640-1550	1543

The IR Spectrum of Lignocaine Hydrochloride reveals the presence of major functional group in the structure of Lignocaine Hydrochloride supporting its identity.

3. Compatibility Studies:

FTIR Studies:

Infra-red spectroscopy is one of the most powerful analytical techniques to identify functional groups of drugs. IR spectroscopy was conducted using a Fourier transform IR spectrophotometer (FTIR Bruker, Japan) and the spectrum was recorded in the wavelength region 4000-400cm-1. The procedure consisted of dispersing a sample alone. The sample was placed in the light path in sample holder, and the spectrum was recorded. The FTIR spectrum of drug is shown in Figure. The peaks observed in Figure are listed in table and can be considered as characteristic peaks of each sample. These peaks were compared with the individual peaks.

The IR spectra of drug and various polymers were recorded in combination with each other.

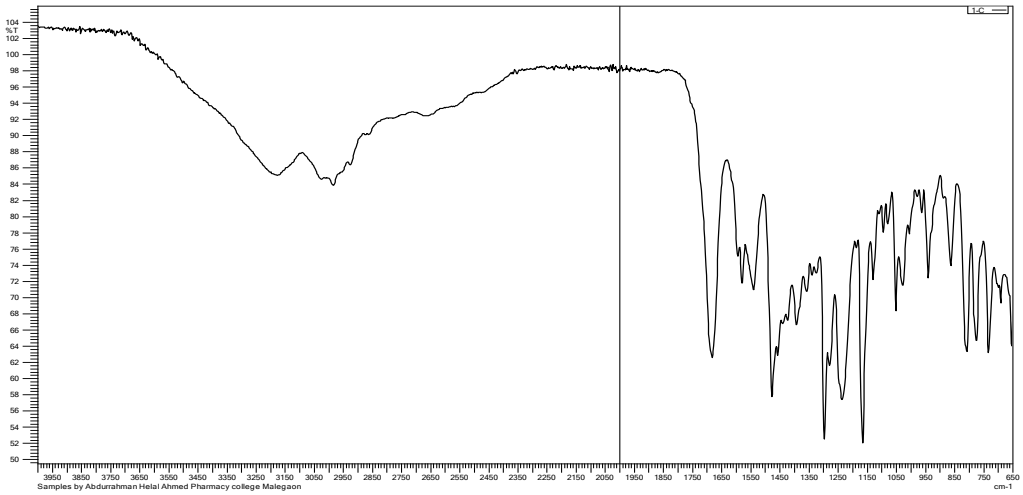

Fig.No.5. IR Spectrum of Sildenafil Citrate, Lignocaine Hydrochloride, Carbopol, Sodium metabi sulphate, Methyl paraben and Propyl paraben

Table No.5. Comparison of Results of FT-IR Analysis of Sildenafil Citrate, Lignocaine Hydrochloride, Carbopol, Sodium metabi sulphate, Methyl paraben and Propyl paraben with the Reported Standards.

Functional Group	Characteristic Peak	Observed Peak
O-H Stretching	3400-3200	3176
C=N	1690-1640	1683
Cl	785-540	713
Amide	1680-1630	1680
S=O	1375-1300	1359

The IR Spectra of Sildenafil Citrate, Lignocaine Hydrochloride, Carbopol, Sodium metabi sulphate, Methyl paraben and Propyl paraben revealed the major functional groups of Sildenafil Citrate hence there was no probable interaction between drug and polymers.

4. DSC of pure drug:

The thermal behavior of Sildenafil Citrate was examined by DSC, using a SHIMADZU DSC-60 PLUS Differential scanning calorimeter. The DSC thermogram of Sildenafil Citrate was typical of a crystalline substance, exhibiting a sharp endothermic peak at 193.72^{0}C. Onset and endset temperature were 192.47^{0}C and 198.15^{0}C. Thermogram is shown in figure.No.8.4.1. Sildenafil Citrate.

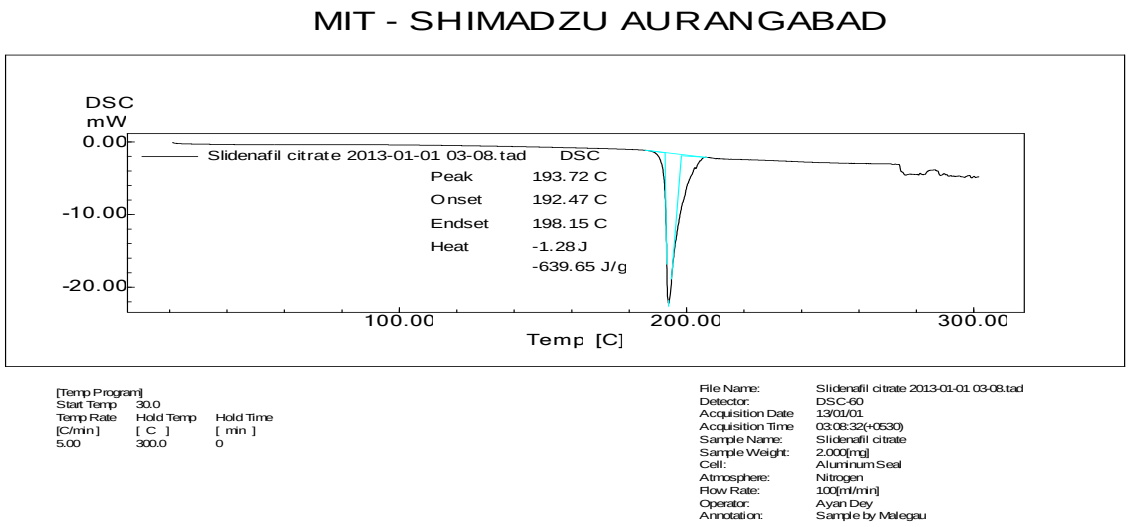

Fig.No.6. DSC of Pure Drug

5. Evaluation Parameters of topical gel formulation batches F1 to F5:

5.1. pH measurement:

Table.No.6. pH measurement of formulation batches of F1 to F5

Batch No.	pH
F1	6.89 ± 0.04
F2	6.91 ± 0.04
F3	6.94 ± 0.03
F4	6.94 ± 0.05
F5	7.00 ± 0.03

5.2. Viscosity measurement:

Table.No.7. Viscosity measurements of formulation batches of F1 to F5

Batch No.	Viscosity (cps)
F1	28832 ± 0.73
F2	29312 ± 1.35
F3	30378 ± 1.25
F4	31564 ± 0.95
F5	32946 ± 0.82

5.3. Spreadability measurement:

Table No.8. Spreadability measurement of formulation batches of F1 to F5

Batch No.	Spreadability(gm.cm/sec)
F1	4.55
F2	6.45
F3	4.10
F4	7.10
F5	5.55

5.4. Homogeneity:

Table No.9. Homogeneity of formulation batches of F1 to F5

Batch No.	Homogeneity
F1	Homogenous
F2	Homogenous
F3	Homogenous
F4	Homogenous
F5	Homogenous

5.5. Percentage drug content measurement:

Table No.10. Percentage drug content measurements of formulation batches of F1 to F5

Batch No.	% Drug Content
F1	98.40 ± 0.30
F2	98.90 ± 0.50
F3	99.10 ± 0.10
F4	99.72 ± 0.72
F5	99.83 ± 0.83

5.6. *In-vitro* Drug Release Measurement:

Table No.11. In-vitro drug release study of formulation batches of F1 to F5

Time (minute)	In-vitro drug release (%) CDR Batch No.				
	F1	F2	F3	F4	F5
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10	0.23 ± 0.84	14.35 ± 0.64	9.64 ± 0.91	9.64 ± 0.40	2.6 ± 0.22
20	16.70 ± 0.44	26.47 ± 0.15	19.29 ± 0.55	20.07 ± 0.60	2.87 ± 0.10
30	36.60 ± 0.65	48.30 ± 0.27	45.65 ± 0.62	36.28 ± 0.30	45.07 ± 0.11
40	50.95 ± 0.98	77.77 ± 1.33	60.89 ± 0.85	46.58 ± 0.50	62.66 ± 0.24
50	75.72 ± 0.73	89.89 ± 1.03	74.13 ± 1.14	73.58 ± 0.60	80.67 ± 0.50
60	96.63 ± 0.76	98.14 ± 0.73	92.15 ± 0.79	92.76 ± 0.80	99.09 ± 0.42

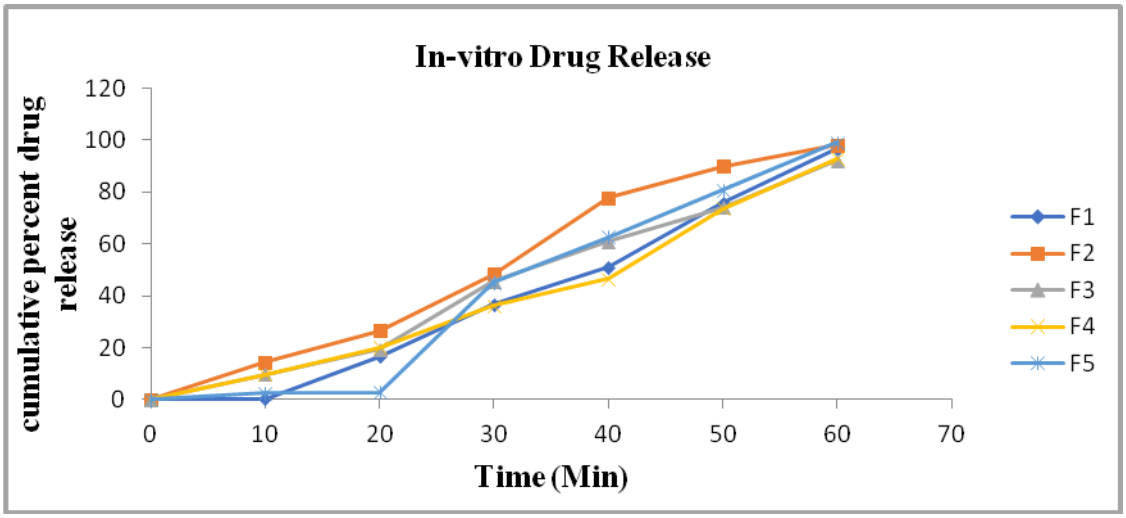

Fig.No.7. %Cumulative Drug Release of All Batches

The total amount of drug released for a fixed period of 1 hrs was found to increase with increase Carbopol gelling agent concentration. The in-vitro drug release of F5, F2, F1, F4, F3 gel formulation can be ranked at 1 h according to their drug release values as follows: (99.09 ± 0.42 %) > (98.14 ± 0.73 %) > (96.63 ± 0.76 %) > (92.76 ± 0.80 %) > (92.15 ± 0.79 %). A result showed that as the concentration of Carbopol increases, the in-vitro drug release of gel formulations increases. The Formulation batch F5 containing 1.5 g Carbopol maximum release than the other formulation batches.

The drug release data were evaluated by the "Kinetic Release Treatment" software. In-vitro release data were fitted to various mathematical models such as zero order, first order, Higuchi and Korsemeyer-Peppas model in order to understand the mechanism of drug release and the release rate from dosage forms. Table 8.4.7. illustrates the correlation of dissolution data to different models of release kinetic. This result indicated that most formulations exhibit diffusion mechanism in drug release accompalished by acceptable regression value for Higuchi Kinetic model. Kinetic model which best fit Higuchi equation was most suitable for sustained release formulation.

6. Pharmacokinetic Drug Release study:

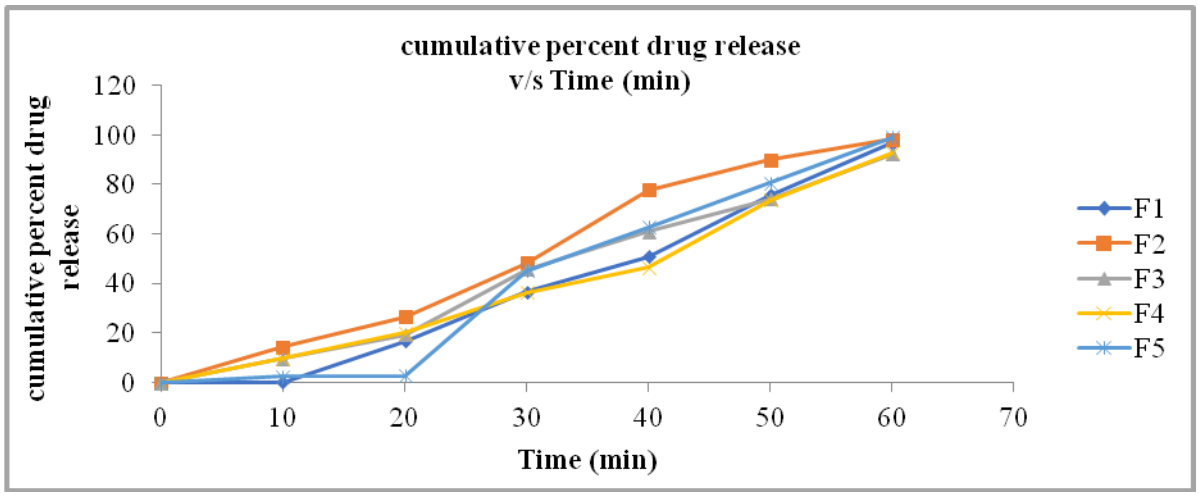

Fig.No.8. Zero order drug release mechanism of formulation batches F1 to F5

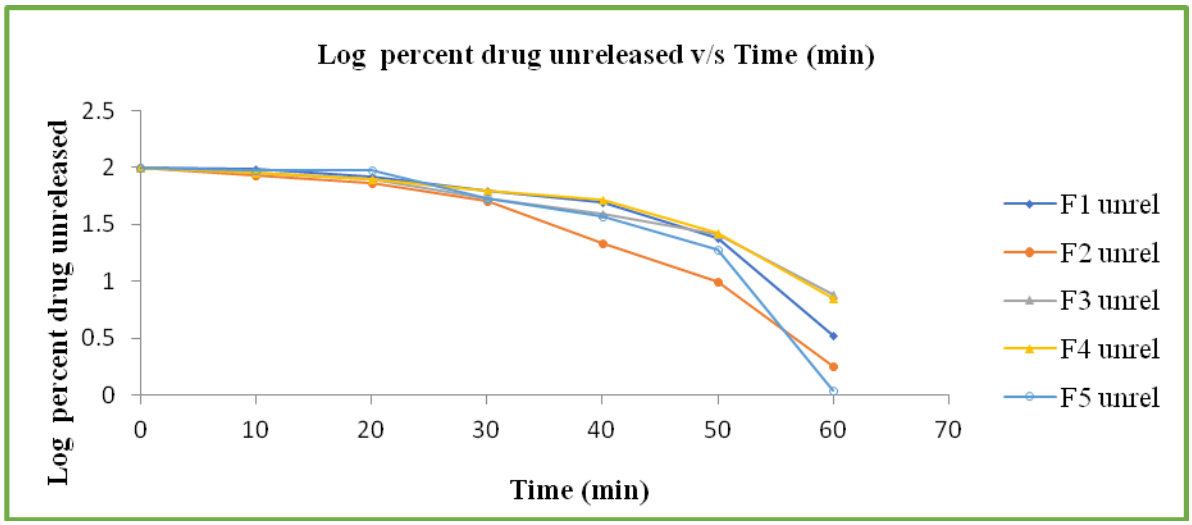

Fig. No.9. First order drug release mechanism of formulation batches F1 to F5

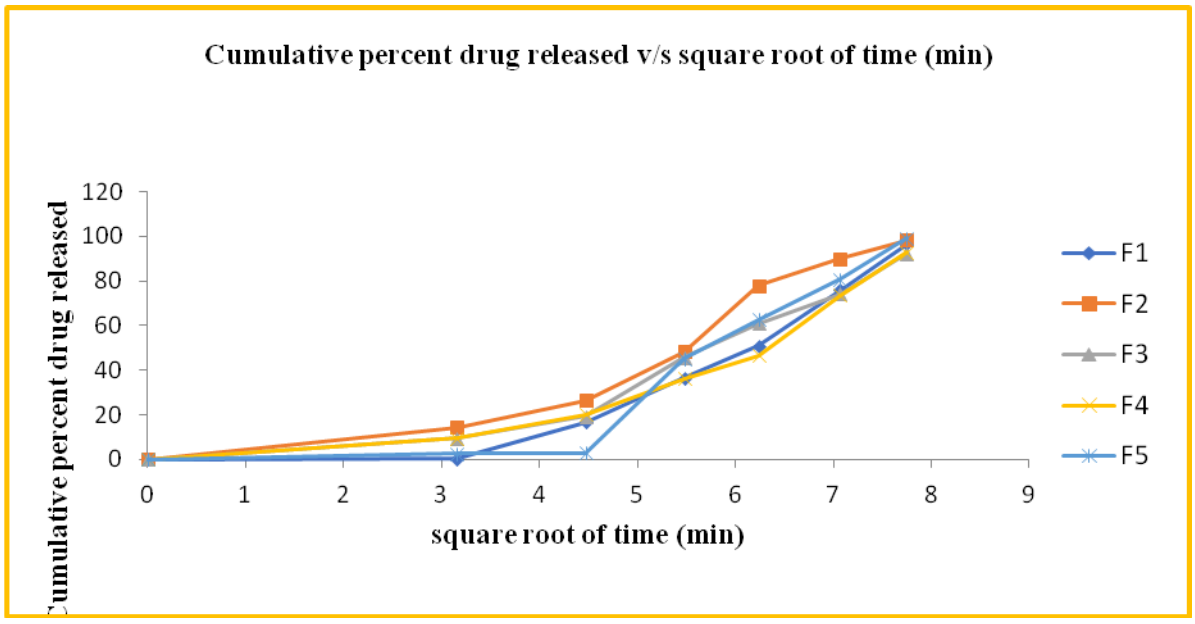

Fig. No.10. Higuchi drug release mechanism of formulation batches F1 to F5

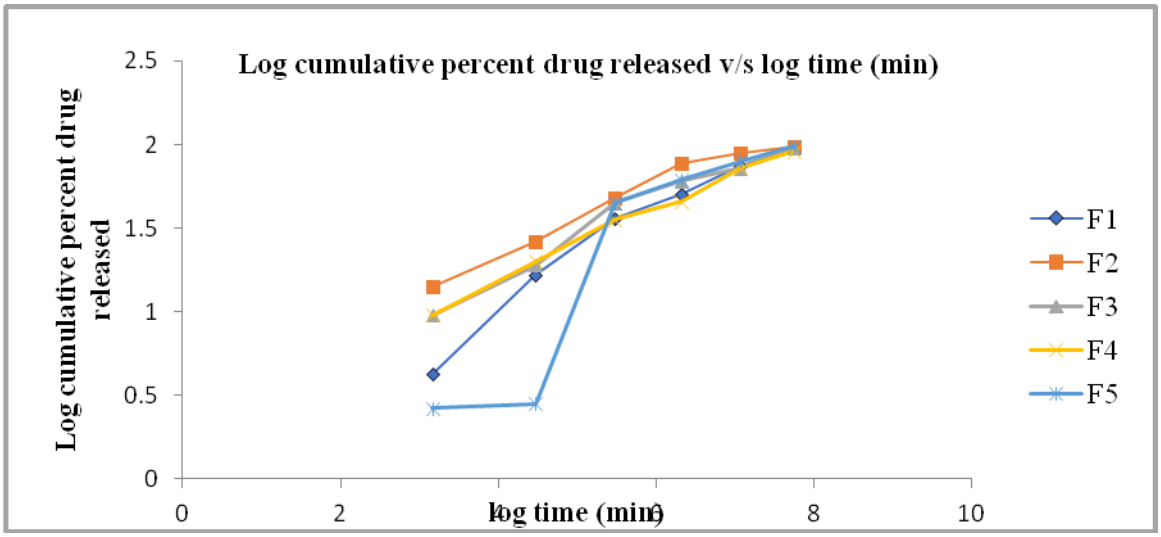

Fig. No.11. Korsmeyers and Peppas drug release mechanism of formulation batches F1 to F5

Table No.12. Regression coefficient (r2) different kinetic models of formulation F1 to F5:

Formulation	Regression			
	Zero Order	First Order	Higuchi	Korsmeyer
F1	0.7886	0.7393	0.9870	0.9578
F2	0.8771	0.8599	0.9796	0.9658
F3	0.8588	0.8655	0.9860	0.9681
F4	0.8172	0.7902	0.9808	0.9928
F5	0.7594	0.7165	0.9870	0.8529

The in-vitro drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order, higuchi and korsmeyer model in order to determine the mechanism of drug release. The results of linear regression analysis data including regression coefficient are summarized in table no.12.

When the regression coefficient 'r' value of zero order and first order plots were compared, it was observed that the 'r' values of zero order plots were in the range of 0.7886 to 0.7594 were as the 'r' values of first order plots were in the range of 0.7393 to 0.7165 indicating drug release from all the formulation was not found to follow first order kinetics.

Figure no.11. showed the percent drug released v/s square root of time plots. It was observed that the 'r' values for the Higuchi plots were found to be in the range of 0.98 to 0.9870 for the formulation study indicated the good release of drug from these formulations. Hence the best fitted model for all the formulations were found to be Higuchi model.

6. Stability Study:

The selected formulations were subjected to the accelerated stability at 40 ± 2^0C / 75 ± 5% RH for three months and evaluated for their pH, viscosity, spreadability, Homogeneity, Drug content and in-vitro drug release studies.

Table No.13. In-vitro drug release study of formulation batches of F1 to F5

Time (minute)	In-vitro drug release (%) CDR Batch No.				
	F1	F2	F3	F4	F5
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10	0.23 ± 0.84	14.35 ± 0.64	9.64 ± 0.91	9.64 ± 0.40	2.6 ± 0.22
20	16.70 ± 0.44	26.47 ± 0.15	19.29 ± 0.55	20.07 ± 0.60	2.87 ± 0.10
30	36.60 ± 0.65	48.30 ± 0.27	45.65 ± 0.62	36.28 ± 0.30	45.07 ± 0.11
40	50.95 ± 0.98	77.77 ± 1.33	60.89 ± 0.85	46.58 ± 0.50	62.66 ± 0.24
50	75.72 ± 0.73	89.89 ± 1.03	74.13 ± 1.14	73.58 ± 0.60	80.67 ± 0.50
60	96.63 ± 0.76	98.14 ± 0.73	92.15 ± 0.79	92.76 ± 0.80	99.09 ± 0.42

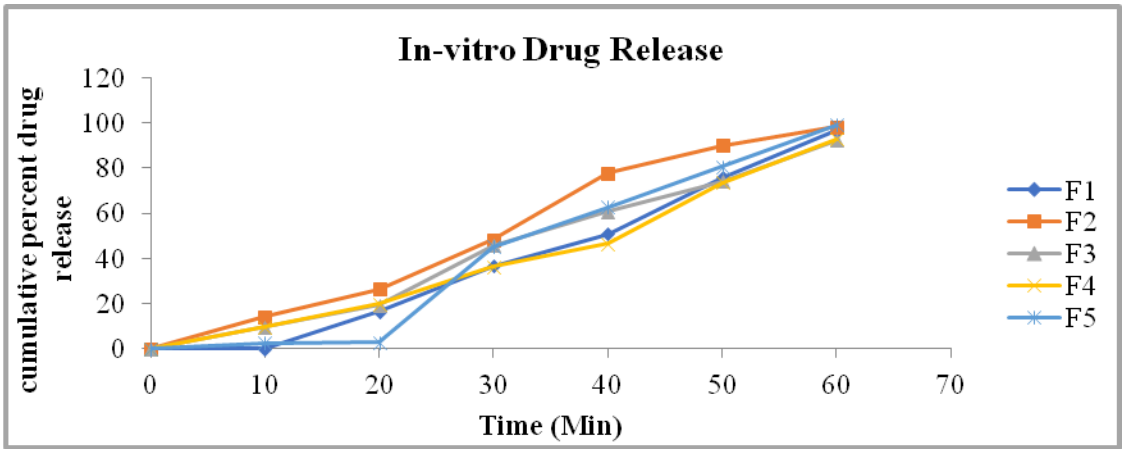

Fig.No.12. %Cumulative Drug Release of All Batches

From the above observation it is concluded that the all parameters complies their initial data. Hence the formulation are stable after three month at 40 ± 2^{0}C / 75 ± 5% RH.

CONCLUSION:

Sildenafil Citrate is the drug of choice in the treatment of premature ejaculation. Topical gel of Sildenafil Citrate was prepared with aim to deliver the drug through topical rout as it provide quick onset of action in comparison of oral rout in preliminary study Carbopol-934 and Lignocaine were evaluated for their efficiency to form a gel.

Different parameters were carried out for topical gel formulation. The polymer Carbopol was found to be suitable candidate as it gives better consistency, viscosity, spreadability, pH, homogeneity and in-vitro drug diffusion.

Carbopol concentration was optimize trial and error method. Result showed that in-vitro drug diffusion increase addition of high amount of Carbopol in topical gel formulation. So it was concluded that Carbopol is effective diffusion enhancer in the treatment of premature ejaculation.

Further topical gel of Sildenafil Citrate can also be prepared by using different gel forming polymer and natural permeation enhancer to produce economical enhancer.

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