Pharmacophore 2016, Vol. 7 (4), 292-308 USA CODEN: PHARM7 ISSN 2229-5402

Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Original Research Paper

FORMULATION AND EVALUATION OF MICROSPONGE BASED DRUG DELIVERY SYSTEM OF LEVONORGESTREL

Monika A Madane*, Ajay D Shinde

Dept Of Pharmaceutics , Svpm's College Of Pharmacy, Malegaon (Bk) Svpm's College Of Pharmacy, Malegaon (Bk)

ABSTRACT

The aim of present work is to prepare microsponge of Levonorgestrel using Carbopol 934 as a polymer. Emergency contraception (EC) is a method of contraception that is used to prevent pregnancy after an act of unprotected sexual intercourse. It is known by several other names *e.g.* 'morning after' or post-coital method. Levonorgestrel microsponge were prepared using quashi emulsion solvent diffusion method. In order to standardize the microsponge formulation, factor affecting the physical properties of microsponge were determined. The IR, DSC,SEM studies were carried out to study Interaction, shapes, morphology of microsponge and thermal analysis respectively. In vitro release study also studied in 0.1N HCl and 0.1% SLS solution to study the release kinetics.and the Stability study also studied.

Keywords: Microsponge, Contraception, Quashi-Emulsion Solvent Diffusion, SEM, DSC.

INTRODUCTION

Emergency contraception (EC) is a method of contraception that is used to prevent pregnancy after an act of unprotected sexual intercourse. These methods are for one time use following a contraceptive accident and are effective if used within a short time frame after sexual exposure. As the name signifies, it is meant only for contraceptive emergency situations and not for routine or repeated use.

Recently the drug delivery systems use to treat contraception are pills ,vaginal ring , the Patch ,Shot/Injection ,Implantable Rods ,Intrauterine Devices ,Sterilization Implant , Surgical Sterilization were still acceptable, such dosage form are no longer sufficient to overcome the various contraception methods. Which are conventionally use from many years, which also have number of limitations out of these limitation the most important is residence time of drug at the site of application. To overcome these limitations there is need to find some innovative featured microsponge drug delivery in the contraception method.

Microsponge is recent novel technique for control release and target specific drug delivery system. Microsponges are polymeric delivery system composed of porous microspheres. They are tiny sponge-like spherical particle with a large porous surface. Microsponge system offers entrapment of ingredient and is believed to contribute towards reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. Microsponge systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as gel, cream, liquid or powder and have recently been used for oral administration.

Levonorgestrel, as contraception, is a progestogen that causes thickening of cervical mucus, inhibition of sperm capacitation or survival, and alteration of the endometrium. Levonorgestrel, as an emergency contraceptive, prevents ovulation or fertilization by altering tubal transport of sperm and/or ova, as well as inhibiting implantation by altering the endometrium. The Levonorgestrel formulations are available in the market are Plan B, Unwanted Pills, Levonorgestrel Emergency Contraceptive, My Way, Next Choice. The main mechanism of action of Levonorgestrel when used for regular contraception is prevention of fertilization. In addition and in contrast to the hormonal methods, Levonorgestrel also has an effect on the uterine fluid/ endometrium which is likely to contribute to the high contraceptive efficacy It also gives the targeted drug release effect.

The current research topic undertaken to formulate and evaluate the microsponge based drug delivery sysyem of Levonorgestrel by Quashi-emulsion solvent diffusion method, which ultimately helps to improve the bioavalability of drug, and gives the sustain and contral release effect which will ultimately improve the birth control.

MATERIALS AND METHODS

Materials: Levonorgestrel was received as gift sample from Famycare Labs Pharmaceutical Pvt.Ltd Ahamadabad (India), Carbopol 934,PVA, Ethanol, was obtained from Loba Chemie Pvt. Ltd. Mumbai. All other chemical and reagent were of analytical grade.

Instrument: Three bladed stirrer, Dissolution apparatus, Stability Chamber, SEM, DSC.

8. Experimental Work:

8.1 Optimization of Analytical Method[64-70]

8.1.1Preparation of Calibration Curve for Levonorgestrel:

A.Standard Calibration Curve of Levonorgestrel in water:

Appropriate dilution of the standard stock solutions was done; working standard solutions of suitable concentrations of Drug were prepared by diluting 1 to 10 mL up to 10 mL to get working standard solution of 1-10 µg/ mL. The standard solutions were then scanned in the spectrum mode of the instrument from 400 nm to 200 nm and their spectra were overlaid. Absorbance at λ max 242 was noted. The absorbance of different concentration of Levonorgestrel is reported in below:

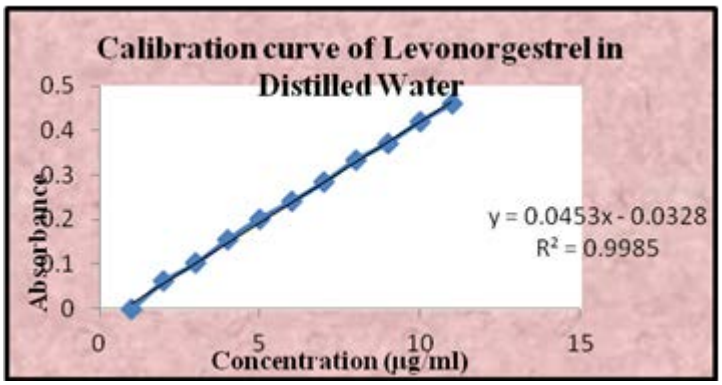


Fig :Standard Calibration Curve of Levonorgestrel in water

B.Standard Calibration Curve of Levonorgestrel in 0.1 N HCl:

Appropriate dilution of the standard stock solutions was done; working standard solutions of suitable concentrations of Drug were prepared by diluting 1 to 10 mL up to 10 mL to get working standard solution of 1-10 µg/ mL. The standard solutions were then scanned in the spectrum mode of the instrument from 400 nm to 200 nm and their spectra were overlaid. Absorbance at λ max 242 was noted. The absorbance of different concentration of Levonorgestrel is reported in below:

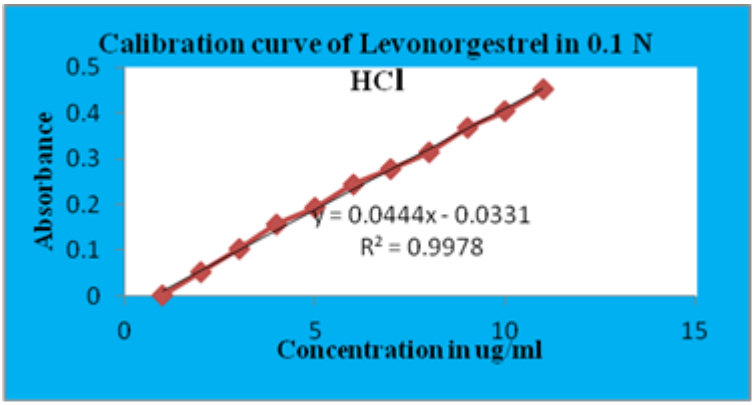


Fig 6:Calibration curve of Levonorgestrel in 0.1 N HCl

C.Standard Calibration Curve of Levonorgestrel in Methanol

Appropriate dilution of the standard stock solutions was done; working standard solutions of suitable concentrations of Drug were prepared by diluting 1 to 10 mL up to 10 mL to get working standard solution of 1-10 µg/ mL. The standard solutions were then scanned in the spectrum mode of the instrument from 400 nm to 200 nm and their spectra were overlaid. Absorbance at λ max 242 was noted. The absorbance of different concentration of Levonorgestrel are reported in below:

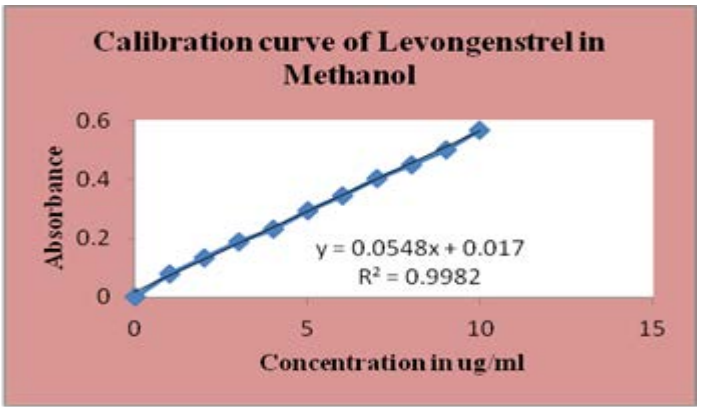


Fig :Calibration curve of Levonorgestrel in Methanol

. Validation:

1.Linearity:

From above solutions (A) sample was pipette out 1 ml solution and made 1-10µg/ml concentration with dilution of Distilled water. Absorbance was checked of these concentration for linearity. Levonorgestrel was shows the maximum absorbance at wavelength 242 nm in Distilled water. The result obtained was shown in fig.

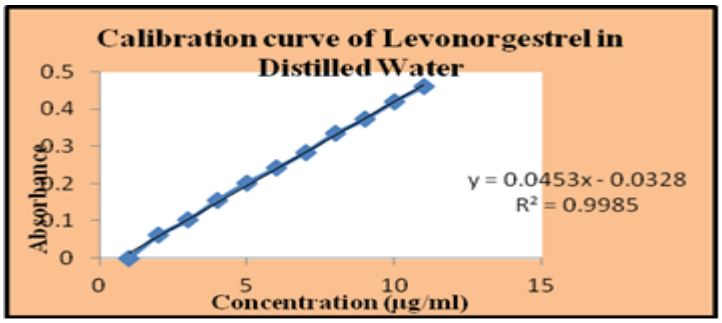


Fig : Calibration curve for Levonorgestrel in Distilled water

2. Precision:

Precision of developed method is demonstrated by intra-day and inter-day validation.

I. Intra-day Precision:

The six replicate absorbance of fixed concentration 10 µg/ml was recorded and from which the Standard Deviation (SD), Relative Standard Deviation(%RSD), Mean was calculated. Absorbance checked at λmax 242 nm. Reported in observation table.

Sr No.	Conc.	λ max	Absorbance
1	10	242	0.46
2	10	242	0.461
3	10	242	0.462
4	10	242	0.460
5	10	242	0.459
6	10	242	0.46
Mean			**0.460333333**
S.D			**0.001032796**
%RSD			**0.224358195**

Table : Intra-day Precision

II. Inter-day Precision:

The assay procedure was carried out for 3 days with freshly prepared solution from stock solution at fixed concentration i.e 10 µg/ml in six replicate at 24 hours interval. Absorbance was recorded from which Standard Deviation (SD), % Relative Standard Deviation (RSD), Mean was calculated. Absorbance was checked at λmax 242 nm. Reported in observation table.

Sr No.	Conc	λ max	Abs 1	Abs 2	Abs 3
			1st Day	2nd Day	3rd Day
1	10	242	0.46	0.46	0.461
2	10	242	0.461	0.461	0.462
3	10	242	0.462	0.462	0.462
4	10	242	0.46	0.46	0.459
5	10	242	0.462	0.459	0.461
6	10	242	0.46	0.46	0.46
Mean			0.4608333	0.460667	0.460833
S. D			0.0009832	0.001211	0.001169
% RSD			0.2133509	0.262893	0.253681

Table : Inter-day Precision

3.Accuracy:

Accuracy was conducted at three different levels 80%, 100%, 120% then solution was prepared in 8µg/ml, 10µg/ml, 12µg/ml concentrations. This concentration considered as 80%,100%,120% respect

Sr No	Conc	λ max	Absorbance	Mean	S.D	RSD	%RSD
1	80	242	0.36	0.35	0.01	0.028571	2.857143
2	80	242	0.35				
3	80	242	0.34				
1	100	242	0.46	0.456667	0.005774	0.012643	1.264271
2	100	242	0.45				
3	100	242	0.46				
1	120	242	0.58	0.583333	0.005774	0.009897	0.989743
2	120	242	0.59				
3	120	242	0.58				

Table : Accuracy

4.Robustness:

Firstly 10 µg/ml concentration sample was prepared from standard solution B, taken absorbance of the solution at two different wavelength. and calculate Mean, Standard Deviation(SD), %Relative Standard Deviation(%RSD). Reported in observation table

A. Absorbance at λmax -2 nm (240nm)

Sr.No	Conc	λ max	Absorbance	Mean	S.D	RSD	%RSD
1	10	240	0.355	0.355	0.001	0.002817	0.28169
2	10	240	0.354				
3	10	240	0.356				

Table : Robustness at λmax -2 nm (246nm)

B. Absorbance at λmax +2 nm (244nm)

Sr.No	Conc	λ max	Absorbance	Mean	S.D	RSD	%RSD
1	10	244	0.557	0.557333	0.001528	0.002741	0.274077
2	10	244	0.559				
3	10	244	0.556				

Table : Robustness at λmax +2 nm (250nm)

8.3 Formulation and Development

8.3.1 Factorial Design

Factorial Batches for Carbopol-934 and Polyvinyl Alcohol:

A 2^2 factorial design was implemented for optimization of combination optimum polymeric formulation. According to the model it contained 2 independent variables at 2 levels, +1,-1. According to model total four formulations are possible, the composition of different formulation are shown in Table.19 The different independent variables, Carbopol-934 were (X_1) and Polyvinyl Alcohol concentration (X_2).

Batches Code	Variable Level in Coded Form	
	X1	X2
F1	+1	+1
F2	+1	-1
F3	-1	+1
F4	-1	-1

Table 19: Factorial design for preparation of batches

Sr. No.	Ingredient	Quantity of Ingredients (mg)			
		F1	F2	F3	F4
1	Carbopol-934	1200	1200	800	800
2	Ethanol	15	15	15	15
3	Polyvinyl Alcohol	50	40	50	40
4	Water	200	200	200	200

Table 20: Formulated batches of Microsponge

8.3.2Formulation Method of Microsponges

A. Preparation of Microsponges:[74-83]

The microsponges were prepared by Quashi-Emulsion solvent diffusion method. The method consist of two steps. In first step inner phase was prepared and in second step outer phase was prepared. Inner phase was prepared by dissolving the carbopol-934 as a polymer in 15 ml in ethanol. Then , Levonorgestrel was added to solution and dissolved under ultrasonication at 35^{O}C for 15 minutes. Outer phase was prepared by

dissolving Poly vinyl Alcohol in the distilled water and the process was carried out at room temperature. Then inner phase was then poured into outer phase at room temperature. After emulsification, the mixture was continuously stirred at 500 rpm for two hours. After the formulation of microsponge the mixture is filtered to separate the microsponge . the product was washed and dried in oven at 40^0C.

Initially preliminary batches were prepared by using drug polymer ratio and process was optimized as shown in above Factorial design. In order to study the effect of polyvinyl Alcohol the microsponge are prepared by changing the concentration gives the detail of the formulated batches.

Fig : Microsponge formulation by three bladed stirrer

Fig : Microsponge obtained after Quashi-Emulsion solvent diffusion method

RESULT AND DISCUSSION

A. Preparation of Calibration Curve for Levonorgestrel :

a) Calibration curve of Levonorgestrel in distilled water was found to be linear shown in above graph and coefficient of correlation was found to be 0.998. For the determination of unknown concentration of Levonorgestrel following equation can be used.

$Y= mX + C$; $Y= 0.045x-0.032$; $R^2 = 0.998$

Where Slope was 0.045 and intercept was -0.032.

b) Calibration curve of Levonorgestrel in 0.1 N Hcl was found to be linear shown in above graph and coefficient of correlation was found to be 0.997. For the determination of unknown concentration of Levonorgestrel following equation can be used.

$Y= mX + C$; $Y= 0.044x-0.033$; $R^2 = 0.997$

Where Slope was 0.044 and intercept was 0.033.

B.UV spectrophotometric method development and Validation:

The proposed UV spectrophotometric method has been validated for the linearity, accuracy Precision and robustness. The linearity of measurement was validated by analysing different concentration of the standard solution of Levonorgestrel. The Beer-Lamberts concentration range was found to be 3-18 µg/ml and distilled

water, so this method has good linearity range. The linearity was observed in the expected concentration range which demostrating its suitability for analysis.

%RSD of interday and intraday precision in distilled water was found to be 0.2243 and 0.2133,0.2628,0.2536 respectively as shown in table no.10 and 11 respectively. This % RSD in acceptable limit. the precision was validated repeatability and ruggedness. In Precision Intra-day and Inter-day precision assay results were indicated that the method was capable with high precision.

Accuracy was conducted in distilled water at three different concentration 80%,100%, 120% and result of %RSD was found to be 2.8571,1.2643,0.9897 respectivly as shown in table no.12 The result of accuracy studies was indicated that the method was accurate within the desired range.

The robustness was performed by changing different condition like changing standard wavelength i.e +2 nm and -2 nm. The % RSD was found to be at +2 nm and -2 nm 0.2740 and 0.2816 respectively as shown in Table no.13 and 14 respectively. The result of robustness was indicates no variation in the procedure.

It was concluded that result of all analytical parameter such as a Linearity, Precision, Accuracy and Robustness was found to be significant acceptable limit so that this UV spectrophotometer validated methods was considered for further analytical experimental work.

8.2 Preformulation studies:[52,53,54]

Preformulation study is the process of optimizing the delivery of drug through determination of physiological properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. It gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipient in the dosage form.

8.2.1 Preliminary Properties

a) Organoleptic Properties

The sample obtained was examined for its appearance and color. Results are reported in section 9.2.5

b) Determination of melting point

The melting point of Levonorgestrel was determined by capillary method using Thiel's tube.

8.2.2 Identification of Drug

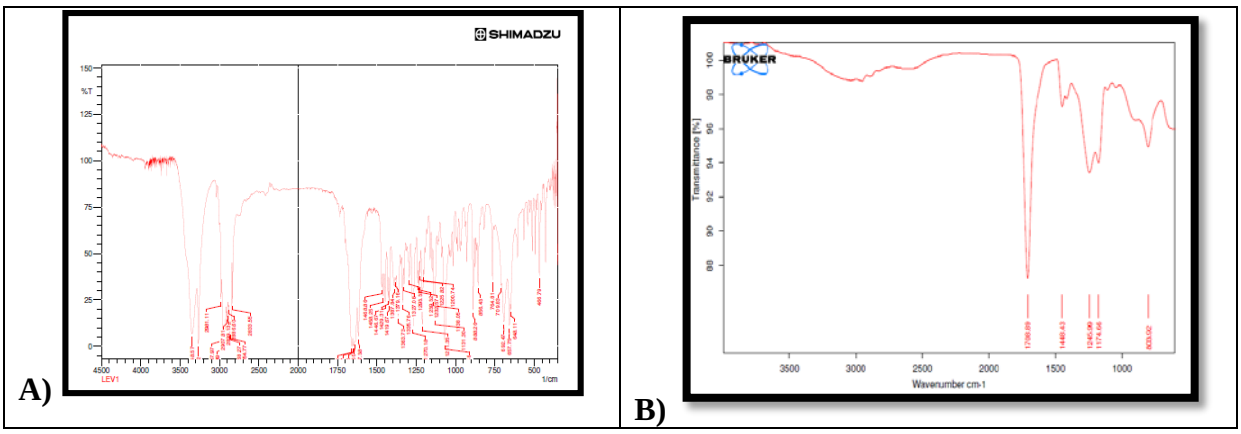
a) IR absorption spectrum

IR Spectroscopy of Levonorgestrel was done by using FT-IR Spectrophotometer (Shimadzu, Brukr). The spectra were scanned over wavelength range of 4000 to 400 cm^{-1} at resolution of 4 cm^{-1}. The KBr pellet techniques were used for the infra-red absorption. The procedure consists of dispersing samples in KBr and compressing into discs by applying a pressure of 5 tons for 5 minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

5 FT-IR Spectroscopy

Fourier Transform Infra-Red Spectroscopy of drug and polymer were recorded on Shimadzu Fourier Transform Infra-Red spectrophotometer using KBr powder. And Brucker Fourier transform Infrared-red spectrophotometer. The instrument was operated under dry air purge and the scans were collected at scanning speed 2mm/sec with resolution of 4 cm^{-1} over region 4500-400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction. The FT-IR a spectra of polymer and complex formulation is shown in figure.

Identification of Drug and Polymer



A) B)

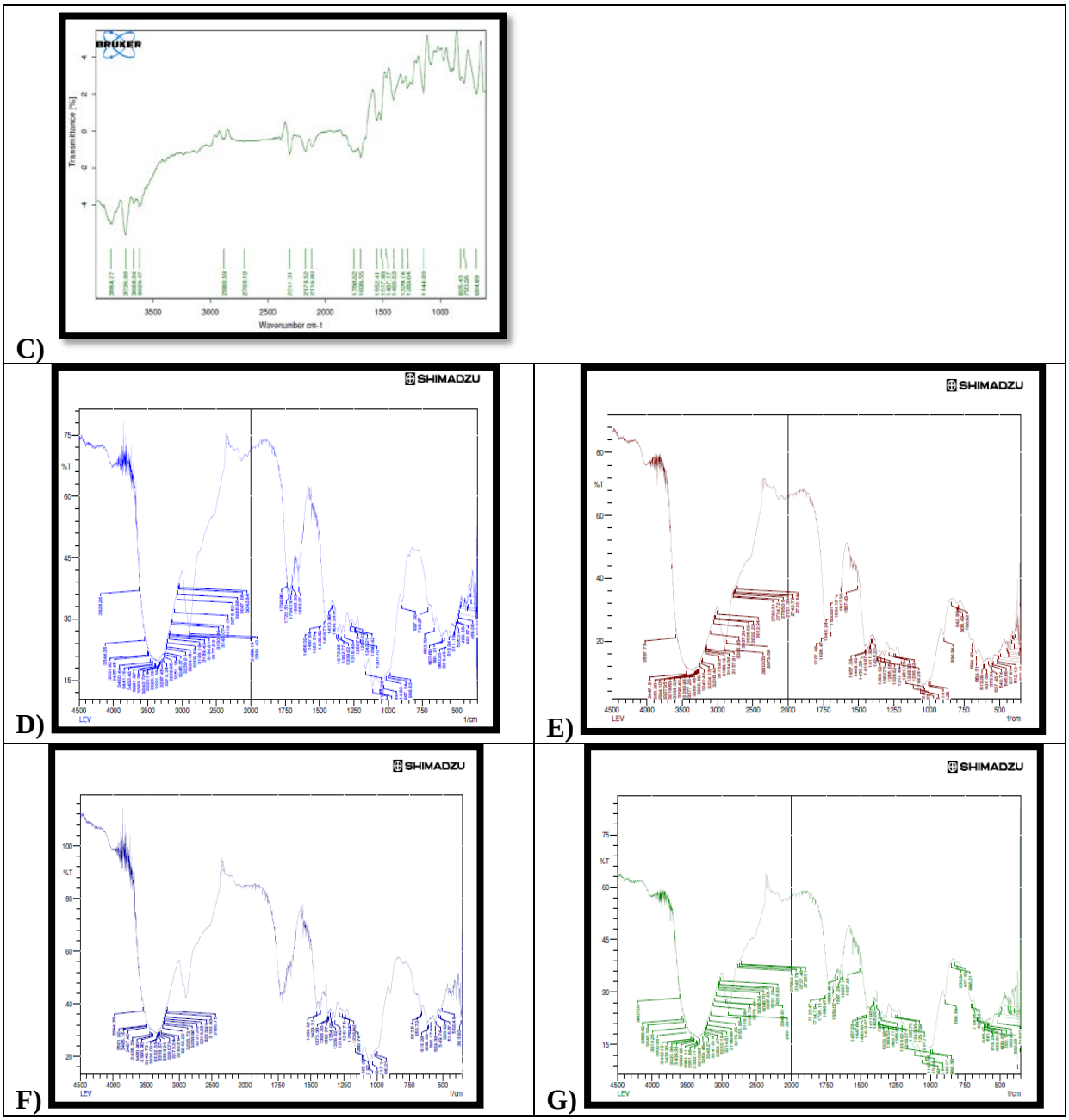


Fig: IR Spectra of Levonorgestrel, carbopol 934,PVA,F1,F2,F3,F4 showing A,B,C,D,E,F,G

DSC of Levonorgestrel

Differential scanning calorimetry was performed for drug on PerkinElmer 4000 instrument. Thermographs were obtained by heating 1 mg samples in aluminum pans at heating rate 100°/min, from 30°C to 350°C, in a nitrogen atmosphere (flow rate 20mL/min). Data was analyzed, using PYRIS Version 11.1.0.0488 software, for origin to obtain onset temperature (Tonset); the peak temperature (T peak) and the endset temperature (T endset) of endothermic peak.

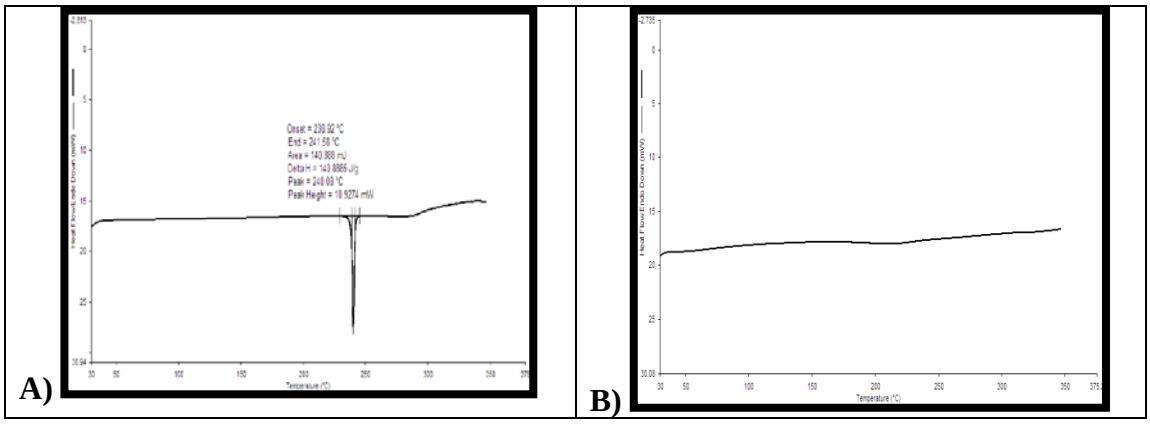


Fig3:DSC of Drug and Formulation F1,F2Showaing A,B,respectively

8.4 Evaluation of Formulation

8.4.1 Loading Efficiency of Microsponge

Accurately weighed 20mg of corbopol 934 loaded microsponge were dissolved in 2 ml dichloromethane, 30 ml of 0.1 N HCL solution was added and the mixture was heated at 50-55ºC for 45 min in thermostatic water bath to remove dichloromethane. After that the volume was adjusted to 50 ml with the same fresh buffer heated at 50-55 ºC. The solution was cooled, filtered diluted and analyzed spectrophotometrically at the 242nm using 0.1 N HCL as a blank. The drug content drug entrapment efficiency of the microsponge were calculated. Realibility of this method was assessed by containing a recovery analysis using amount of the drug with or without polymer.

Sr. No.	Formulation code	Drug content in 100 mg MS Formulation (Practical)	Drug content in 100 mg MS Formulation (Theoretical)	Loading Efficiency of MS (%)
1	F1	20.23	25	80.92
2	F2	21.24	25	84.97
3	F3	23.51	33.33	70.54
4	F4	25.12	33.33	75.37

Table 9: Loading Efficiency of Microsponges

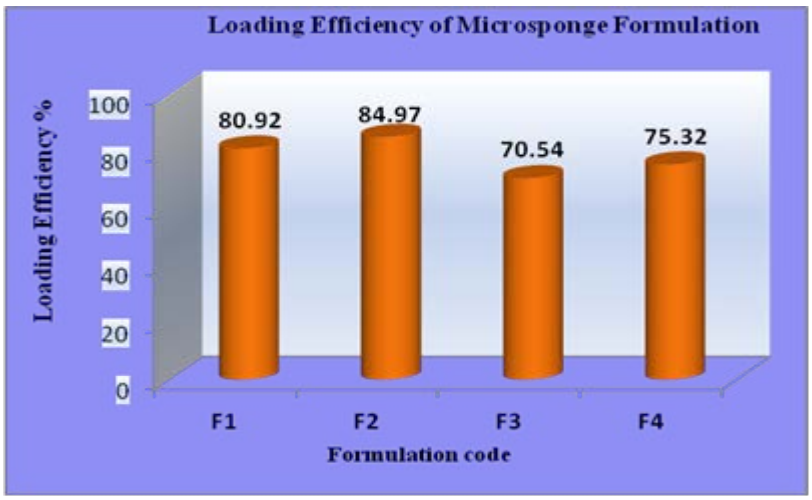


Fig :Loading Efficiency of Microsponge Formulation

8.4.2 Powder Flow Properties

a. Angle of Repose:

The angle of repose was determined by using funnel method. Free flowing powder of microsponge were weigh accurately and poured in to funnel, which can be raised vertically until a maximum cone height, h, is obtained. About 2 gm of sample of each formulation was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured[68].

Angle of repose was calculated by using following formula:

$$\tan\theta = \frac{h}{r}$$

$$\text{Hence} \quad \theta = \tan^{-1}\frac{h}{r}$$

Where, θ = angle of repose, H = height of the cone, r = radius of the cone base.

Angle of Repose	Flowability
<20	Excellent
20-30	Good
30-34	Acceptable
>40	Very Poor

Table : Relationship between Angle of repose and flowability

b. Tapped Density:

Approximately 2 gm of powder of each formulation was introduced into a 10 ml measuring cylinder. The powder were carefully levelled without compacting it and the apparent volume was measured (V_0). Then cylinder containing sample was attached to the bulk density apparatus and tapped for about 100 times until it gives constant volume[68]. Tapped density was calculated using following formula:

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tap volume in cm}^3}$$

c. Bulk Density:

Bulk density is defined as the mass of powder divided by bulk volume. Approximately 2 gm of powder of each formulation was introduced into 10 ml measuring cylinder. The bulk density was calculated by dividing weight of sample in grams by bulk volume[68]. Bulk density was calculated using following formula:

$$\text{Bulk Density} = \frac{\text{Weight of powder in grams}}{\text{Bulk volume of powder in cm}^3}$$

d. Hausner Ratio:

It provides an indication of the degree of densification. Lower the Hausner ratio better is the flow property[68]. It was calculated using following formula:

$$\text{Hausner Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Hausner ratio	Flowability
<1.18	Excellent
1.19-1.25	Good
1.3-1.5	Acceptable
>1.5	Poor

Table : Correlation between Hausner ratio and Flowability

e. Carr's Compressibility Index:

This is an important property in maintaining uniform weight. It was calculated using following formula:

$$\% \text{ Compressibility} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Sr. No.	Carr's Index	Type of Flow
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair
4	23-30	Poor
5	33-38	Very poor
6	>40	Extremely poor

Table : Relation between the Carr's index of Powder and its Flow Characteristics

8.4.3Particle size and size distribution

The particle size was determined using an optical microscope. The microscope was fitted with a stage micrometer to calibrate the eyepiece micrometer. On slide sprinkle some Levonorgestrel microsponge powder and measure the particle size by calibrating the optical eyepiece micrometer.

Calibration of the eyepiece micrometer

One division of the stage micrometer = 0.01mm = 10µm

C = (SM X 100) / EM

Where C = correction factor

SM = Reading of stage micrometer which coincides with reading of eye-piece micrometer (EM). The particle diameters of around 100 microsponges were measured at random with optical microscope.

The average particle size was determined using the equation

D (mean) = Σnd / Σn

Where n = No of microspheres observed, d = mean size range.

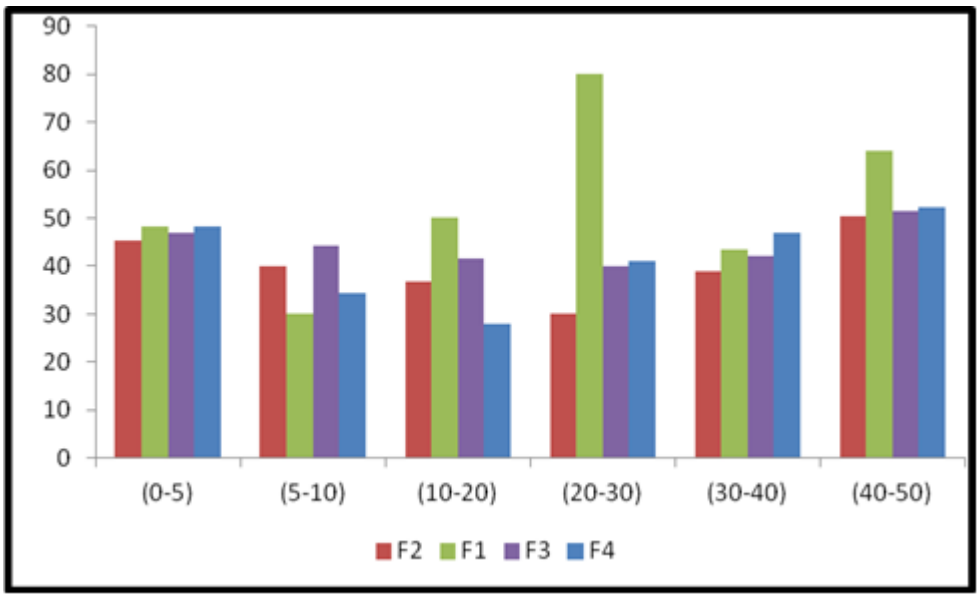


Fig:Frequency of Partical Size distribution of Levonorgestrel Microsponges

8.4.4 SEM study of Optimized Microsponge Formulation of Levonorgestrel:[82,83]

Prepared microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the microsponges can be studied by scanning electron microscopy (SEM). SEM of a fractured microsponge particle can also be taken to illustrate its ultrastructure.
The surface morphology of Microsponge examined using FEI : NOVA NANO SEM 450 Instrument at Savitribai Phule University of Pune.

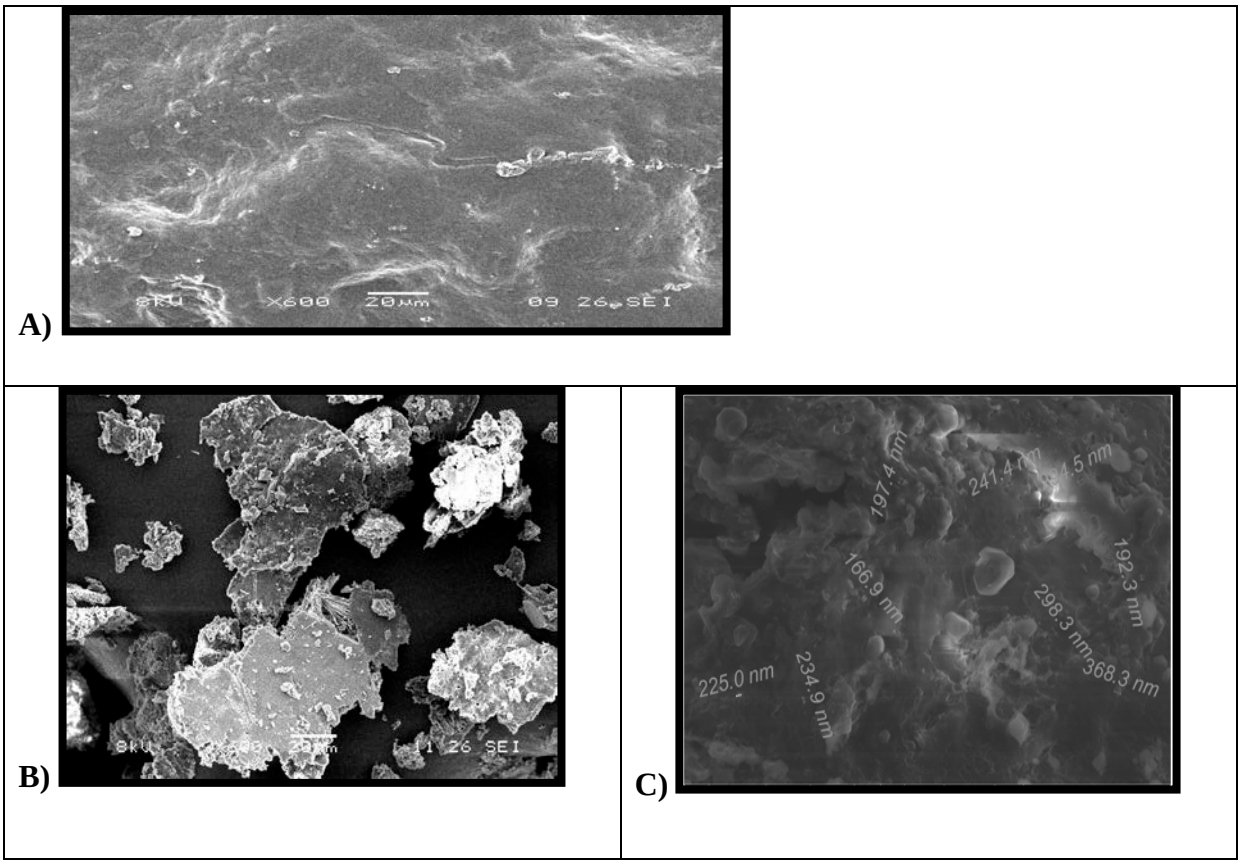


Fig 6: Showing Placebo, Morphology of drug load microsponge and partical size A,B,C respectively

8.4.7 In vitro Release Studies

The approximately 1 mg of dose of Levonorgestrel in microsponge besed drug delivery was placed in 00 size capsule and release rate of 1mg Levonorgestrel from capsule was determined using the United States Pharmacopeia dissolution testing apparatus basket type (Electrolab TDL-08L). The dissolution test was performed using 900ml 0.1N HCl and 1% SLS Solution at 100 rpm at 37±0.5ºC. In the present studies aliquots of 5ml from the dissolution medium were withdrawn at different time interval of 15,30,45,60, 120 up to 360 min and sink condition was maintain by an equal volume of fresh dissolution medium. The samples analysed for Levonorgestrel content by measuring its absorbance at 242nm using Shimadzu 1700 UV-Visible spectrophotometer with proper dilution. The % cumulative drug release of drug was calculated.

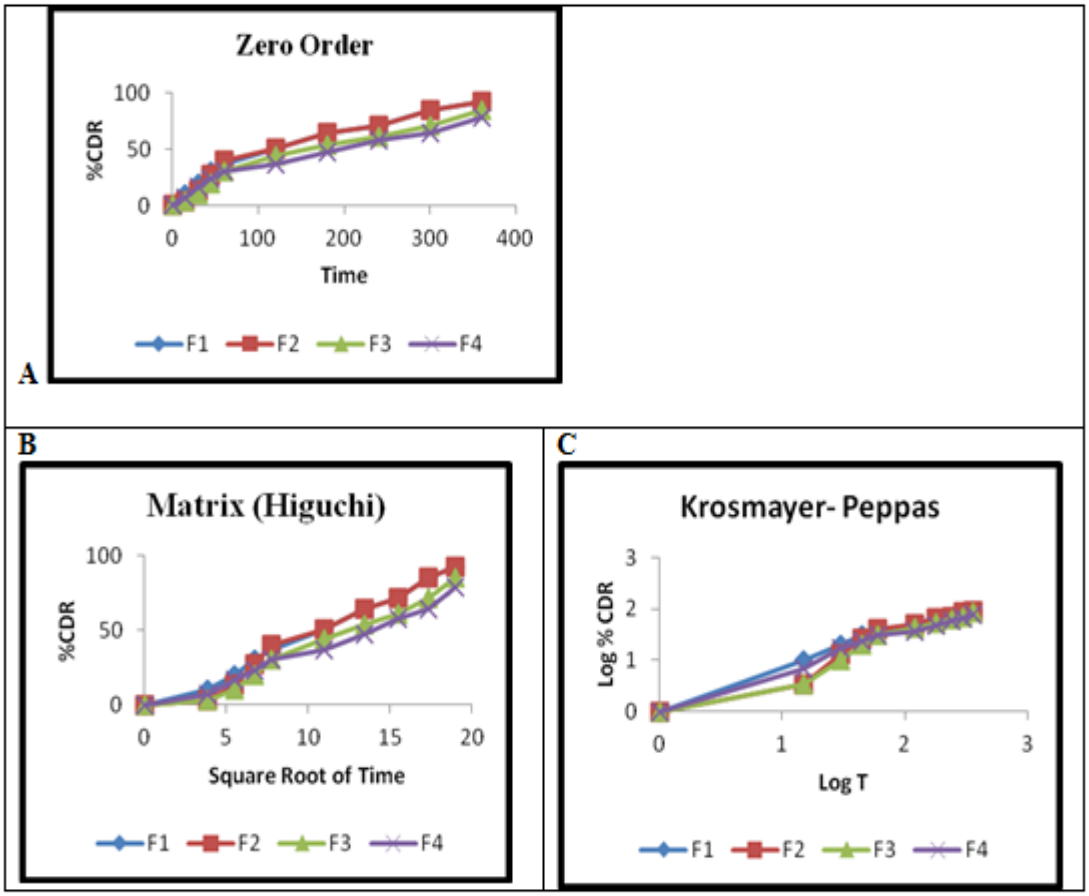


Fig : dissolution study zero order, Matrix(Higuchi),Krosmayer-Peppas A,B,C respectively

8.5.8 Data Analysis of Release Kinetics

Formulation	Zero Order	Higuchi matrix	Peppas Plot	Best Fit Model
F1	0.970	0.991	0.9935	**Krosmayer- Peppas**
F2	0.926	0.973	0.909	**Higuchi matrix**
F3	0.953	0.973	0.936	**Higuchi matrix**
F4	0.953	0.982	0.981	**Higuchi matrix**

Fig : Best model Fit for all Formulation

8.4.10 Regression Analysis:[94]

The effect of formulation variables on the response variables were statistical evaluated by applying ane way ANOVA at O< 0.05 level. To describe the response surface curvature, the design was evaluated by design model, which bears the form of equation and results are reported an chapter IX.

$Y= b0 + b1X1 + b2X2 + b3X1X2 + b4X12 + B5X22$

Where

Y= is the respons variable,

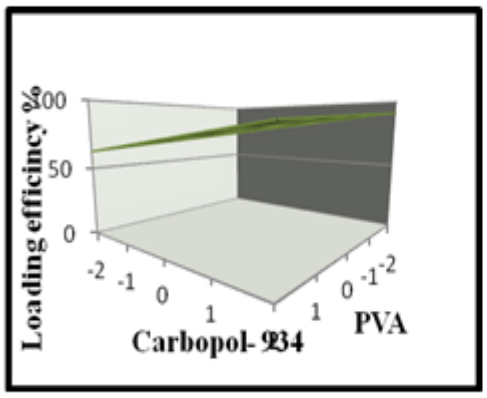
b_0= constant

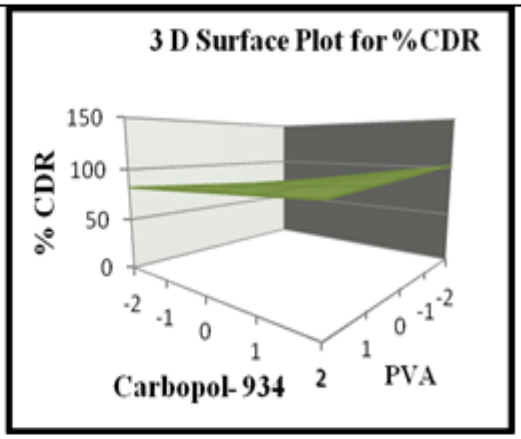
b_1,b_2.....b_5 the regression coefficient,

X_1 and X_2 stands for the main effect,

X_1X_2 are the interaction terms, show how response changes when two factors are simultaneously changed.

% Loading Efficiency of Microsponges Represented by 3D surface plot and % Loading Efficiency of Microsponges Represented by 3D Surface Plot





$Y_1 = 77.95 + 4.995 X_1 - 2.22X_2 + 0.195X_1X_2$

$\%CDR\ Y_2 = 86.527 + 5.197X_1 + 0.1425X_2 - 1.4125X_1X_2$

8.5.9 Stability study of optimized formulation at 40±0.50C; 75%5%RH condition:

1) Loading Efficiency of F2 batch

days	Formulation code	Drug content in 100 mg MS Formulation (Practical)	Drug content in 100 mg MS Formulation (Theoretical)	Loading Efficiency of MS (%)
0	F2	19.88	24.65	80.64
7		21.01	25	84.04
15		22.56	33.33	67.68
30		25.22	33.33	75.66

Table 45: Loading Efficiency of optimized formulation F2

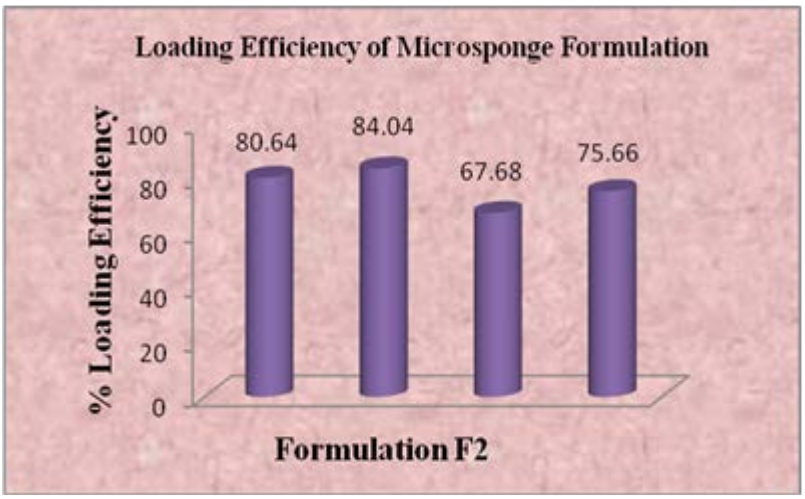


Fig 36 : Loading Efficiency of Formulation in Stability Study

2) In-Vitro Dissolution Study:

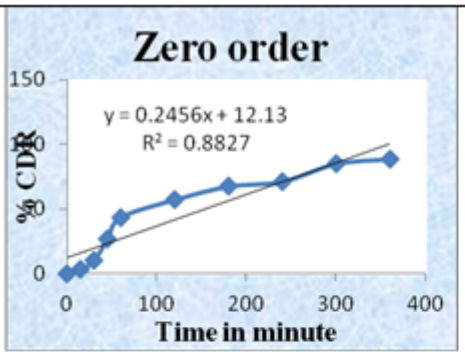


Fig : Zero order kinetics Model

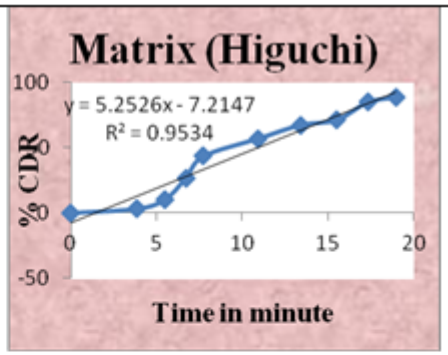


Fig: Matrix Higuchi Model

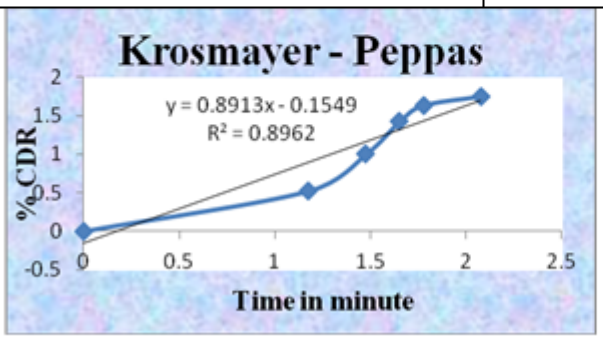


Fig : Krosmayer-Peppas Model

3) Stability Study of optimized batch F2

Time in days	Loading Efficiency Batch (F2)	In-vitro Release Batch (F2)		
		Model	R^2	K/n
0	80.64%	**Zero model**	0.882	0.245
7	84.04%	**Higuchi model**	0.953	5.125
15	66.67%	**Krosmayer-Peppas**	0.896	0.891
30	75.66%			

Table : Stability Study of optimized batch F2

REFERENCE:

1. Gondkar S,Saudager Sinkar N, R, A Review: Microsponge a innovative strategy for drug delivery system current status and future prospects Int J Pharma & lif Sci 2015;5(3):226-243.
2. Gadhave M V, Gaikwad D D, Rajpure P B Shelke P K, , Microsponge Drug Delivery System Int J Uni Pharma & Lif Sci 2013;3(4):1-1
3. Banik A Jain N, Sharma P K, , Recent advance on microsponge delivery system. Int J Pharma Sci Rew & Res 2011;2(8):13-23
4. Manda R, Suthakaran R, A Review Microsponge A Novel Drug Delivery System J Sci Res Pharama 2015;4(1):1-5
5. Suneeta Mittal Emergency contraception - Potential for women's health Indian J Med Res 140 (Supplement), November 2014, pp 45-52
6. Gemzell-Danielsson K, Rabe T Emergency Contraception Journal für Gynäkologische Endokrinologie 2010; 7 (1): 73-77
7. Sally Rafie, Jennifer McIntosh, Debra K. Over-the-Counter Access to Emergency Contraception without Age Restriction Pharmacotheraphy Volume 33, Number 5, 2013 549–557

8. James Simon,Ian Thorneycroft , Pavel Klein,. The impact of antiepileptic drug therapy on steroidal contraceptive efficacy Epilepsy and behaviour 2006(1); 1-9
9. Dhanaraju M D, Kannan R K, Biodegradation and biocompatibility of contraceptive-steroid-loaded poly (dl-lactide-co-glycolide) injectable microspheres: in vitro and in vivo study. Contraception 2006;74:148-156
10. Gopal M,Swetha A, Venkata K, Formulation and In-Vitro evaluation of etodolac entrapped in microsponge based drug delivery system. Int J Pharma 2011;1(2):73-80
11. Lithell H, Effects of Continuous Levonorgestrel Treatment (Subcutaneous Capsules) on the Lipoprotein and Carbohydrate Metabolism in Fertile Women.Upasala J Med Sci 1993;88:103-10
12. Nevado B, Flores R Simultaneous spectrophotometric determination of ethinylestradiol and levonorgestrel by partial least squares and principal component regression multivariate calibration.Analy Chimica Acta 1997;340:257-265
13. Indian Pharmacopoeia. Government of India Ministry of Health and Family Welfare. The Indian Pharmacopoeia Commission. Ghaziabad 2010; (1 and 3): 587, 559, 2103-2105.
14. Sweetman SC. Martindale The complete drug Reference. Pharmaceutical Press London 2009; (36): 1390-1396.
15. https://es.wikipedia.org/wiki/Carbopol
16. Douglas C M. Design and analysis of experiments. John Whiley and Son's; 8th edition:233-292
17. Jain S Pro ultraflexible Lipid Vesicles for effective Transdermal Delivery of Levonorgestrel development, characterization and performance evaluation AAPS Pharm Sci tech 2005:6(3):513-522
18. Joshi D ,Zaidi I, Method development and analytical validation of levonorgestrel drug by RP-HPLC method Int J ad Res Pharma Bio Sci 2014;4(1):1-10
19. Sohrabi M R, Application of Bivariate Calibration Method and Derivative Spectrophotometry to Simultaneous Quantitative Resolution of Ethinylestradial and Levonorgestrel in Pharmaceutical Formulation J App Chem Res 2009;3(10):18-24
20. Ram A Pronisomal Provesicular system for Transdermal Delivery of Hydralazin for Hypertension Asion J Pharm Clin Res 2012;5(3):219-225
21. Jain S Proultraflexible Lipid Vesicles for effective Transdermal Delivery of Levonorgestrel development, characterization and performance evaluation AAPS Pharm Sci tech 2005:6(3):513-522
22. D'souza J Topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system Res J Pharm Tech 2008; 1(4):502-504
23. Gibsona M,Pharmaceutical preformulation and formulation, informa healthcare, second edition; 2009:367-431
24. Kartiika R Formulation and evaluation of Lornoxicam microsponge tablets for the treatment of arthritis Int J Pharm Innov 2013;3(2):29-40
25. Singh R P Nimesulide loaded microsponge in-vitro and ex-vivo evaluation Int J Pharma 2013;4(1):49-60
26. Abdelmalak N A new topical fluconazole microsponge loaded hydrogel preparation and characterization Int J Pharm Pharma Sci 2012;4(1):460-468
27. Baran B E Shanock L.R. Polynomial regression with response surface analysis A powerful approach for examining moderation and overcoming limitation of difference scores. J bus Psychol 2010; 25:543-554
28. Gandhi A Tailoring effect of microsponge for targeted drug delivery J Sciti Innov Res 2013;2(6):1073-1082
29. United state Pharmacopoeia National Formulary. The united states pharmacopoeial convention 2007:277,579
30. www. Access data.fda.gov/scripts/cder/dissolution/dsp get alldata.cfm
31. Dash S, Murty P, Nath L. Kinetic modelling on drug release from controll drug delivery system.Acta poloniae pharmacopoeia Drug Res,2010;67(3): 217-233
32. Patel B, Patel P. Development and validation of stability indicating reverse phase high performance liquid chromatographic method for estimation of levonorgestrel in bulk dosage form.Int J Pharm Drug Anal.2014;2(3):311-318
33. Bhandari A,Kataria M K. Solubility and dissolution enhancement technologies and research emerged Bio Sci Opinion.2013;1(2):105-116

Correspondence Author:

Monika A Madane *

Dept Of Pharmaceutics , Svpm's College Of Pharmacy, Malegaon (Bk) Svpm's College Of Pharmacy, Malegaon (Bk)

Correspondence Author email: Monika30madane@gmail.com

Cite This Article: **Monika A Madane*,** Ajay D Shinde (2016), "Formulation and Evaluation of Microsponge based Drug Delivery System of Levonorgestrel", ***Pharmacophore***, Vol. 7 (4), 292-308.

Covered in Elsevier Products

Pharmacophore

(An International Research Journal)