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Colon-specific tablets containing naproxen microsponges for effective treatment of inflammatory bowel disease

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Abstract---Naproxen is a non-steroidal anti-inflammatory drug, indicated for the relief of inflammation. The aim of the present study was to develop & optimize the microsponges based of naproxen tablet for colon specific drug delivery for enhanced therapeutic effect. Microsponges were developed by quasi emulsion solvent diffusion method. Compatibility of the drug with excipients was studied by FT-IR & DSC .Prepared microsponges were optimized in order to analyze the effects of independent variables (ratio of drug: eudragit (X1), concentration of PVA (X2) & stirring speed (X3)) on the particle size (Y1), entrapment efficiency (Y2) and production yield (Y3) using box behnken design. Particle size (Y1), entrapment efficiency (Y2) and production yield (Y3) were the responses selected for simultaneous optimization, with the aid of Derringer's desirability function. The optimized formulation was subjected to in vitro study. The F1 was selected as optimized formulation based on particle size of 600.75µm , entrapment efficiency of 99.32%, and production yield 94.45% . The results showed that, generally an increase in the ratio of the drug: polymer control release rate of naproxen from micro sponges. Optimized batch of naproxen microsponge was further formulated as tablet formulation for colon delivery. Prepared tablet formulations

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were evaluated for physical parameters like Pre & Post compression evaluation. The drug release data of optimized Batch were fitted into different kinetic models which show that the drug release from tablet formulations follows korsemeyer-peppas release.)

***Keywords*---**naproxen, microsponge, box-behnken design, DFI, tablet.

Introduction

Colon specific drug delivery systems have been the focus of increasing interest due to the importance of this region of the gastrointestinal tract, not only for local but also for systemic therapy. The advantages and necessity of colon targeting for providing more effective therapy to colon related diseases, such as irritable bowel syndrome, colon cancer and inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis have recently been well recognized. Additionally, colonic delivery of drugs may be extremely useful when a delay in drug absorption is required from a therapeutic point of view, e.g. in case of diurnal asthma, angina pectoris & arthritis. Due to absorption or degradation of the API in gastrointestinal. A colon-specific drug delivery system should inhibit drug release in the stomach and small intestine, with a rapid commencement of drug release upon arrival into the colon. Several ways have been explored to transport medications to the colon via the oral route, including coating with pH-dependent polymers, designing time-release dosage forms, and using carriers. They are predominantly destroyed by intestinal bacteria. (1) Every system has advantage as well as disadvantages. Due to manufacturing defects or abnormal stomach physiology, single unit colon focused drug delivery devices may suffer from unwanted breakdown of the formulation & may result in a drug's systemic effectiveness being severely affected & decrease of local therapeutic activity or bioavailability in the colon. Because of its potential benefits like as enhanced bioavailability, reduced risk of local irritation, and predictable stomach emptying, multiparticulate dosage forms have recently received a lot of attention in comparison to single unit systems.(2)

A Microsponge drug delivery system (MDDS) is a patented, highly cross-linked, porous, polymeric microspheres system (10-200 μ in diameter) consisting of porous microspheres particles entrap a wide variety of active ingredients such as anti-infective, antifungal and anti-inflammatory agents etc. (3) It is used mostly for topical and recently for oral administration. The microsponge technology allows an even & sustained rate of release, reducing irritation while maintaining efficacy .Microsponges with a diameter of less than 200 mm are selected by macrophages in the colon. As a result, effective localised pharmacological action may be demonstrated at the desired location. (4)Hence, the present research was intended for developing the microsponges of naproxen by using Design-Expert® software with more loading capacity and better release of the drug The final optimization of naproxen microsponges was done by applying Box-Behnken design.(5). Naproxen is a synthetic, non-steroidal anti-inflammatory medication with a medium potency that is used to treat inflammation and belongs to the BCS II class. Naproxen is an analgesic, anti-inflammatory and antipyretic phenylpropionic acid derivative. The therapeutic benefits of naproxen can last up to 7-8 hours after oral administration, with the commencement of action taking 2 or more hours.(3)

Material and Method

Material

Naproxen powder was supplied by Sun Pharmaceutical Vadodara Gujrat, Eudragit polymers (RS-100) powder were obtained from Yarrow chem product Mumbai, polyvinyl alcohol (PVA) from Loba chemie, India. All other materials used in this study were of analytical grade.

Method

Naproxen loaded microsponge preparation

Preparation of naproxen micro sponge: The micro sponges containing naproxen were prepared by quasi emulsion solvent diffusion method using an internal phase that consisted of Eudragit RS-100, 100 mg and dibutyl phthalate (1% w/v) dissolved in 5 ml of dichloromethane: ethanol (1:1). Glycerol 4% was added to enhance the plasticity of the polymer. This was, followed by the addition of naproxen 100 mg dissolved under ultrasonication at 35°C. The mixture was then poured into 50 ml of aqueous solution of polyvinyl alcohol 60 mg which served as the external phase with 2 hrs stirring at 1000 rpm. The microsponges were formed due to the removal of dichloromethane and ethanol from the system by evaporation. The microsponges were washed with water, filtered and dried at 40°C for 12 hrs and weighed to determine production yield and stored for further investigations .(3)

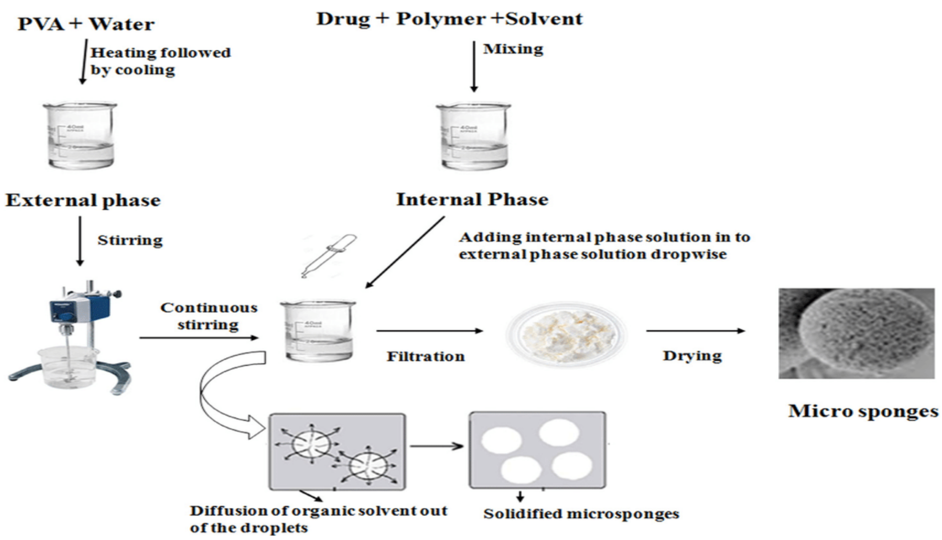

Fig 1 .Formulation of microsponge by QESD method

Experiment design (Response surface methodology/Box-Behnken design) & Optimization

During preliminary trials, it was observed that drug/polymer ratio, amount of PVA & stirring speed had a significant effect on the critical properties of microsponges. The Box Behnken design was used to investigate the extent of the effect of change in independent variables on key product characteristics. The drug/polymer ratio (X1), amount of PVA (X2) & stirring speed (X3) were selected as an independent variable whereas particle size (Y1), % entrapment efficiency (Y2), % production yield (Y3) were selected as response variables. The experimental design parameter & designed batches given in table no 1 & table no 2 respectively

Table 1
Experimental design parameter

Factors	Actual Value			Levels used (Coded Value)		
	Low	Medium	High	Low	Medium	High
Drug : Polymer ratio (Naproxen : Eudragit RS100)	100:100	100 :200	100: 300	-1	0	+1
Amount of PVA	40	50	60	-1	0	+1
Stirring Speed	800	1150	1500	-1	0	+1

Table 2
Experimental runs suggested by the Box Behnken design

Run	Independent Variable		
	X1	X2	X3
	Drug :Polymer ratio (Naproxen : Eudragit RS100) mg	B:PVA mg	C : Stirring Speed RPM
B1	+1	0	-1
B2	0	0	0
B3	0	0	0
B4	0	+ 1	-1
B5	0	- 1	-1
B6	0	0	0
B7	+1	+1	0
B8	0	- 1	+1
B9	+1	0	+1
B10	0	+ 1	+1
B11	- 1	-1	0
B12	- 1	0	-1
B13	-1	0	+1

B14	+1	-1	0
B15	-1	+1	0

3D Response Surface Plots & Contour plot

The potential relationship between three variables studied by the 3D surface and 3D wireframe plots.

Desirability Criteria

The desirability lies between 0 and 1 and it represents the closeness of a response to its ideal value.

Optimization

Particle size analysis

The particle size determination of microsponge formulation was measured using Zetatrac particle size analyzer after appropriately diluting with doubled distilled water (Microtrac, Inc., Montgomeryville, PA, USA) .

Entrapment Efficiency

Naproxen loaded microsponges theoretically equivalent to 10 mg of naproxen were weighed, crushed and extracted with 5 ml of methanol by vortexing. The sample was centrifuged at 2000 rpm for 10 min, filtered and assayed spectrophotometrically at 331 nm after appropriate dilution with methanol. Entrapment efficiency was determined by using formula.

$$\text{Drug Encapsulation efficiency} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

% Practical yield

The % practical yield was determined by taking the ratio of the total weight of the non-volatile raw materials to the final weight of the dried microsponges. The formula for calculation of % practical yield is given below:

$$\text{Practical yield} = \frac{\text{Practical mass (weight of dried microsponges)}}{\text{Total mass (drug + polymer + plasticizer)}} \times 100$$

Drug loading efficiency

$$= \frac{\text{(Mass of drug in microsponge)}}{\text{Mass of microsponge}} \times 100$$

In Vitro Drug Release Study of Microsponges

Drug release was performed by using the USP-II apparatus. The dissolution test was performed using 900 mL of Phosphate buffer (pH 7.4) at the 37±.5 C and 150

RPM. Aliquots were withdrawn at predetermined interval times for 8 h from the dissolution medium and replace immediately with fresh medium. The amount of drug present in the sample was measured by the absorbance of the solution at λ max 331 nm using UV- Visible spectrophotometer. The cumulative percentage of drug release is calculated using an equation obtained from a standard curve.

Statistical analysis of data, Optimization and validation of experimental design

Statistical Analysis

The effect of independent variables on the dependent variables were estimated by using DoE software (Design Expert Trial Version13., Stat-Ease). Polynomial equations were generated for the dependent variables particle size, entrapment efficiency, % production yield .The optimized formulation was selected on the basis of particle size & high entrapment efficiency & production yield and maximum desirability.

Characterization and evaluation of microsponges
Drug and Excipients interaction study

Drug–excipient interactions were investigated by FTIR and DSC studies. IR spectra were recorded to compatibility of drug with excipients, using FTIR spectrophotometer. DSC helps in assessing physical properties of the sample nature (crystalline or amorphous) and indicates any probable interaction among drug and excipients. Naproxen and physical mixture (Naproxen and Eudragit RS 100) were subjected to thermal analysis.

FTIR spectra

FTIR spectra were recorded (FTIR Bruker Alpha I.R. instrument (Germany) using Opus 7.0 software) over wavelength range of 4000 to 500 cm^{-1} at resolution of 4 cm^{-1}. Samples were dispersed in KBr and compressed in pellets by applying 5 tons pressure for 5 min using hydraulic press. Formed pellets were kept in light path and spectra were recorded. Fig 2,3, 4 ,5,6 contain FTIR of drug ,polymer & microsponge.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) About 5 mg of the sample was sealed in the aluminum pans and heated at the rate of 10 °C /min, covering a temperature range of 40 °C to 400 °C under nitrogen atmosphere of flow rate 10 ml/min and DSC thermogram (Shimadzu DSC -60) for pure drug, drug with eudragit RS 100, Drug with PVA & Drug with polymeric mixture was obtained. Thermogram were recorded using lab solution software. Fig no 7, 8,9,10, 11 contain DSC of drug, polymer & MS.

Surface morphology and rheological characterization

The optimized microsponge formulation (MS) was visualized by scanning electron microscope (SEM,) to assess the morphological changes in the microsponge and its surface. The samples were coated with gold under argon atmosphere using gold sputter module in a high vaccum evaporator (Sputter Coater unit VG Microtek, West Sussex, UK) and observed under various magnifications. Microsponges were also evaluated for angle of repose, Hausners ratio and Carr's compressibility index. Fig No 12 contain SEM of Naproxen.

Colon specific tablet
Preparation of colon specific tablet

Preparation and characterization of tablet components
Specific weight of selected prepared microsponges equivalent to 250 mg of naproxen. 1% magnesium stearate as a lubricant, and croscarmellose as super disintegrant, starch, MCC, lactose was mixed well using mortar and pestle for 15 min, then undergo physical evaluation before compression. Before the preparation of tablets, the powder mixtures were evaluated for angle of repose, bulk density, tapped density and compressibility

Table 2
Composition of colon targeted tablet of Naproxen

Ingredient (mg)	Quantity	Category of Excipient
Microsponge	250	Act as API
Starch	10.5	Diluent
MCC	70	Binder
Directly compressible lactose	3.75	Excellent compressibility properties.
Magnesium .stearate	1.75	Lubricant
Croscarmellose	14	Superdisintegrant

Preparation of coating solution

The naproxen tablets were further coated with Eudragit S-100 solution. 2.5 % w/v of coating solution of Eudragit S-100 was prepared in a mixture of Isopropyl alcohol: acetone (1:1). The coating of the matrix tablets was performed by immersion in the coating solution followed by dip coating technique.(6)

Evaluation of Tablet
Pre compression Evaluation [(7)]
It consist of

- **Angle of repose:** The angle of repose of microsponge was determined by the funnel method
  $\tan\theta = h/r$,
  Where θ = angle of repose, h = height, and r = radius.
- **Determination of bulk density and tapped density**
  Bulk density is defined as ratio of total mass of powder to the bulk volume of powder. Tapped density is the ratio of total mass of the powder to the tapped volume of the powder.
  $Db = M/ Vb$,
  Where M is the mass of powder and Vb is the bulk volume of the powder

$Dt = M/ Vt$

Where M is the mass of powder and Vt is the tapped volume of the powder.

- **Hausner Ratio**

  The Hausner ratio is a number that is correlated to the flowability of powder. It is calculated by the following formula:

  Hausner ratio = Dt / Db.

  Where Dt is the tapped density and Db is the bulk density.

  A Hausner ratio greater than 1.25 is considered to be an indicator of poor flowability.

- **Carr's index**

  It indicates powder flow properties. It is expressed in percentage and is given by

  $I = (Dt - Db) \times 100$,

  Where Dt is the tapped density of the powder and Db is the bulk density of the powder.

Post compression Evaluation [(8, 9)]

- **Hardness:** The hardness at which the tablet crushes is the hardness of the tablet.

  Hardness of the 3 tablets from each batch was measured using Monsanto hardness tester. Generally

  Maximum 5 k/sq.in Hardness is required.

- **Friability**

  Roche friabilator is used to evaluate the ability of the tablet to withstand abrasion.

  Pre-weighed 10 tablets were placed in the friabilator, which was then operated for 100 revolutions

  For 4 min. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

  $$F = \frac{W1 - W2}{W1} \times 100$$

  Where F represents the percentage weight loss, and W1 and W2 are the initial and final tablet weights, respectively.

- **Thickness and Diameter**

  Tablet Thickness and diameter were accurately measured by using digital vernier caliper in mm

- **Weight variation**

  USP weight variation test was done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average weight variation tolerance.

- **Content uniformity**

  Weigh accurately a quantity of the mixed contents of the 20 tablet equivalent to 200 mg of naproxen add 10 ml of water and allow standing for 10 min with occasional stirring. Then add methanol to produce 100 ml and filter. To 5 ml of the filtrate, mixtures of equal volume of methanol and phosphate buffer pH 7.4 to produce 100 ml measure the absorbance of resulting solution at maximum at about 331 nm.

- **Dissolution test**
  In vitro drug release studies were performed using USP dissolution test apparatus (Type II). The dissolution studies were performed at 100 rpm at 37±0.5 °C in pH 1.2 pH for first 2 hrs, 6.8 pH for 8 hrs and pH 7.4 for rest of studies. Aliquots were withdrawn periodically and replaced with fresh medium & analyzed at 331 nm.
- **Kinetic data analysis [(10)]**
  Analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order describes the systems where drug release rate is independent of its concentration. The first order describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The following plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) and log cumulative % drug release vs. log time (korsmeyer model).

Table 3
Equation of Kinetics model

Sr.no	Model	Equation
1	Zero order	$Q = Q0 + K0\ t$
2	First order	$\text{Log } Ct = \text{Log } C0 – k\ t\ /\ 2.303$
3	Higuchi diffusion model	$Q = A\ [D\ (2C - Cs)\ Cs\ t]^{1/2}$
4	Hixson-Crowell release model	$Q0^{1/3} – Qt^{1/3} = KHC\ t$
5	Korsmeyer-peppas equation	$Mt\ /\ M\alpha = K\ tn$

Result and Discussion

Drug & excipient compatibility
FTIR

FTIR show the IR spectra of naproxen and physical mixture of drug and polymers. FT-IR spectral data were used to ensure no chemical interaction and to confirm the chemical stability of naproxen in the physical mixture.

Table 4
FTIR ranges

Sr.no	Functional Group	Ranges (cm^{-1})
1	C = O (carboxyl group)	1725.6
2	C–O	1176.5
3	C = C (aromatic stretch)	1602.9
	-CH3 bend	1457.2
4	O–H (carboxylic acid	2968.1

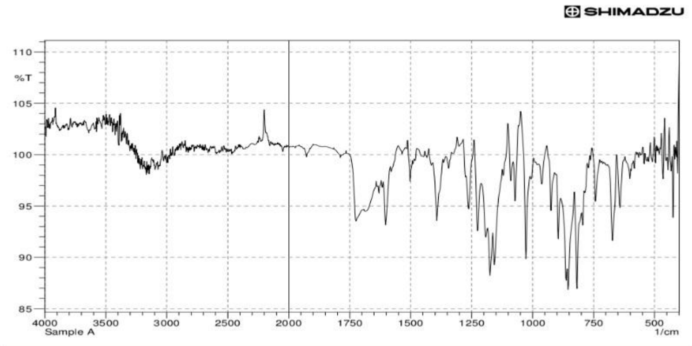

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Fig 2. FTIR of Naproxen

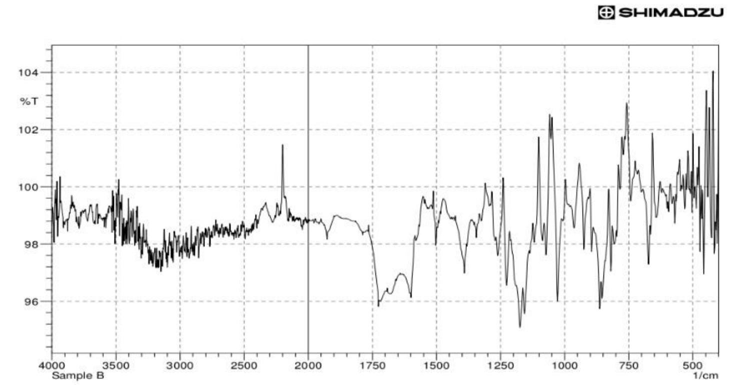

Fig 3. FTIR of Naproxen & Eudragit RS100

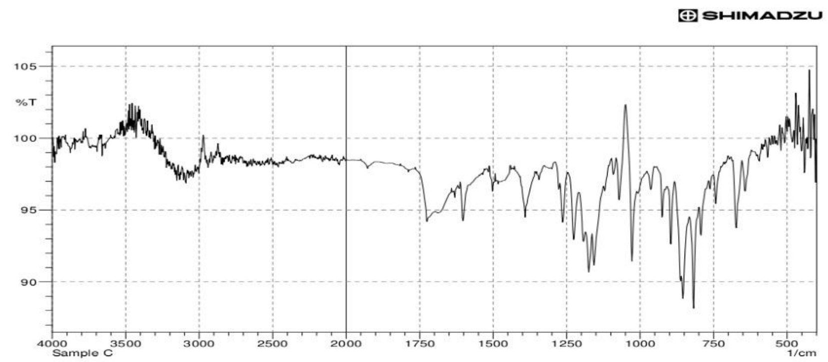

Fig 4. Naproxen & PVA

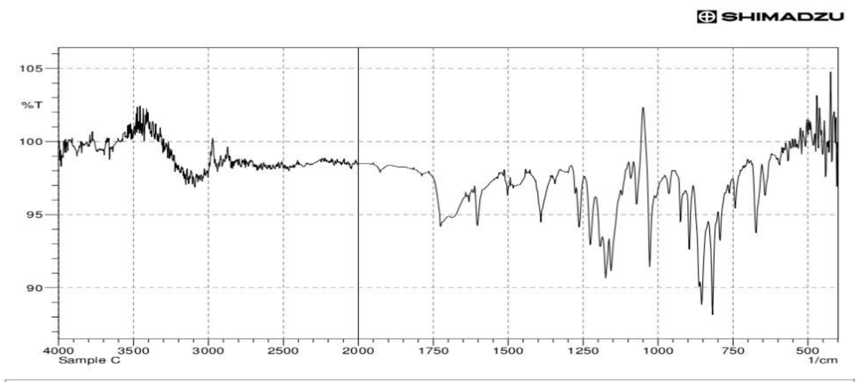

Fig 5. FTIR of drug & polymeric mixture

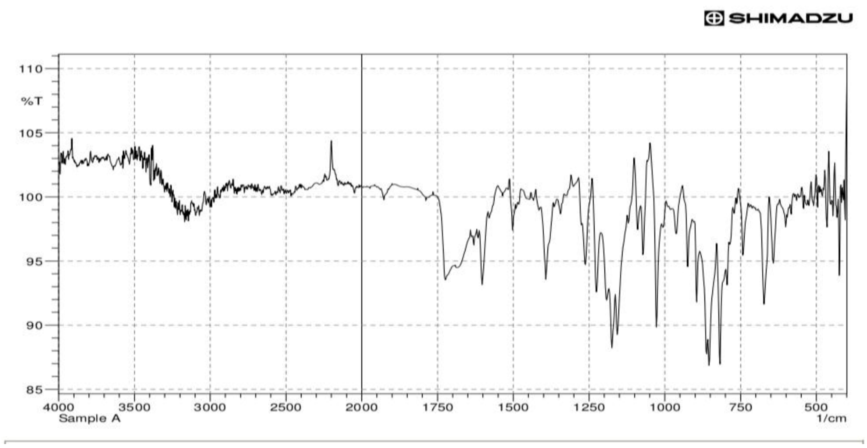

Fig 6. FTIR of Microsponge

Thermal analysis by Differential scanning calorimetry

DSC of the Naproxen, Eudragit RS-100, PVA & microsponge was carried out to check possible interaction in between drug and polymer. DSC graph showed endothermic peak which is indication of presence of drug. In DSC graph of endothermic peak was observed as shown in fig.7

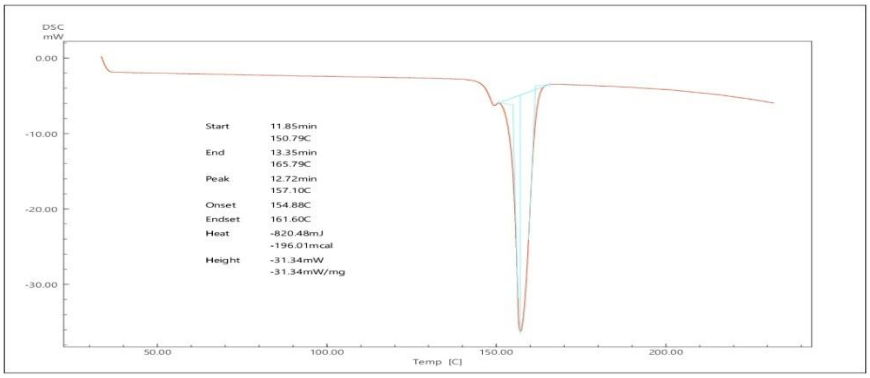

Fig 7. DSC of Naproxen

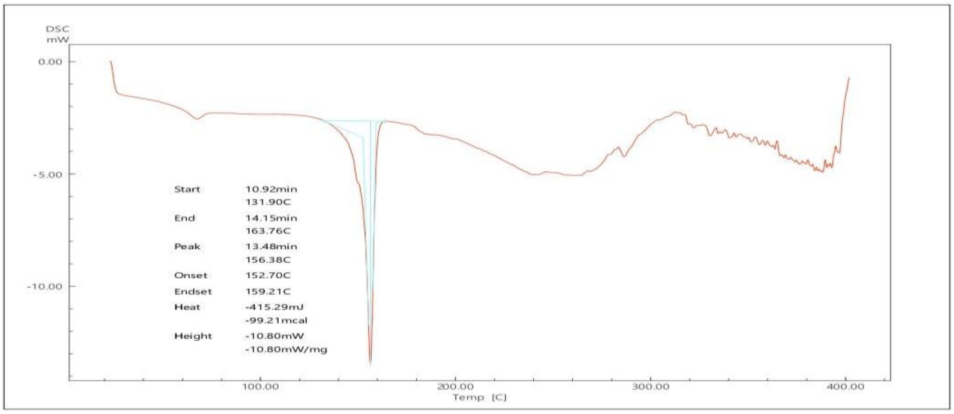

Fig 8. DSC of Naproxen + Eudragit RS 100

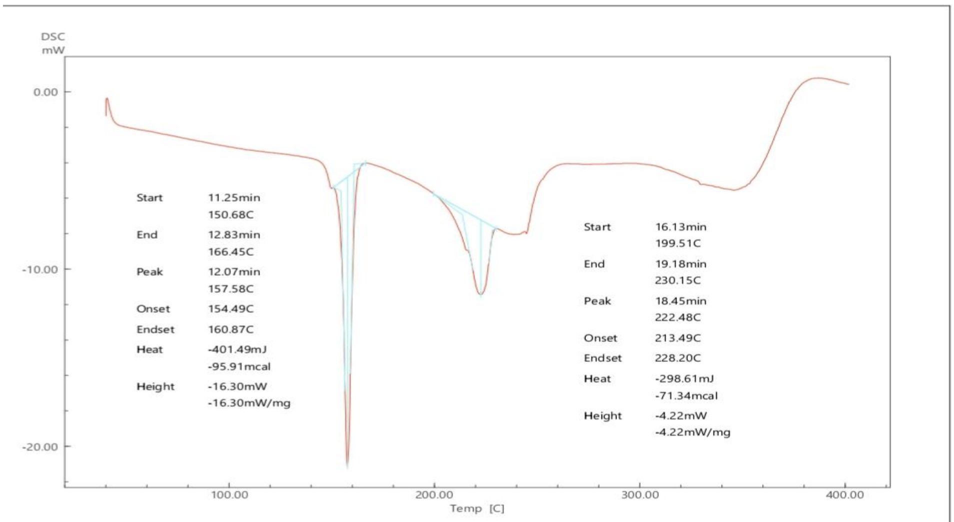

Fig 9. DSC of Naproxen + PVA

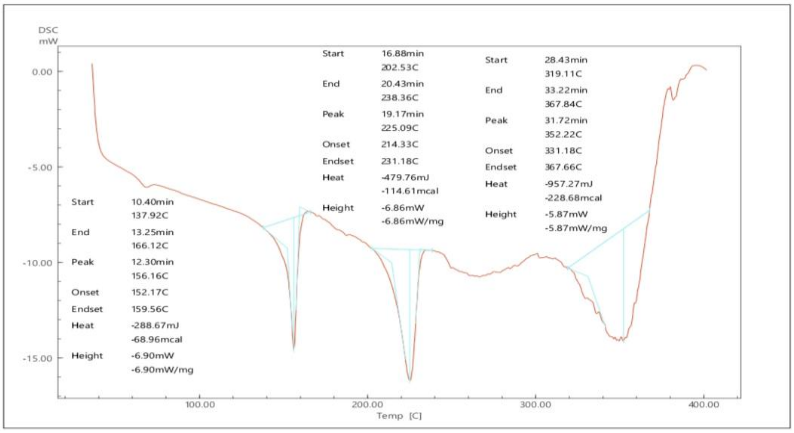

Fig 10. DSC of Naproxen with polymeric mixture

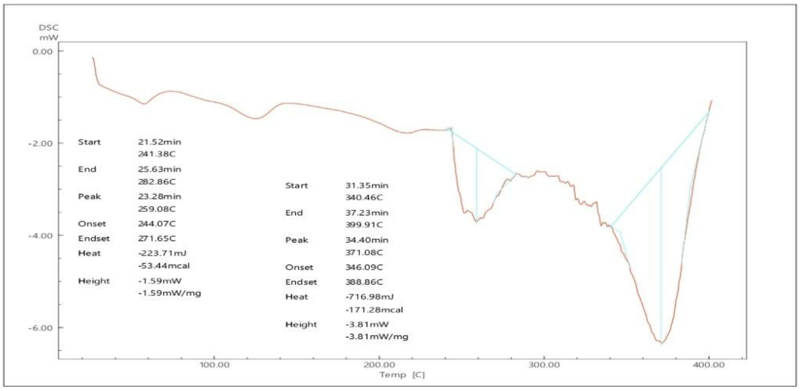

Fig 11.DSC of Microsponge

Scanning Electron Microscopy

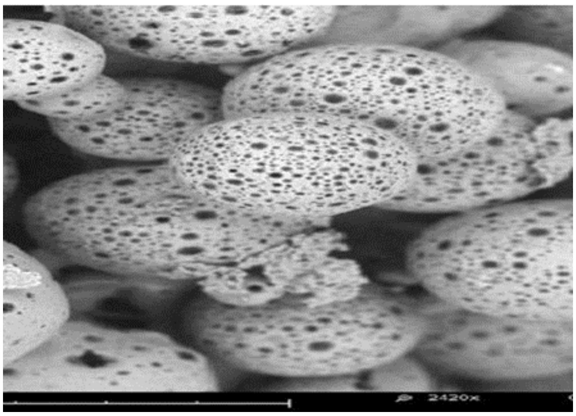

Fig 12. SEM of Naproxen microsponge

Result of designed batches

Mechanism of forming microsponges

The quasi-emulsion method for forming microsponges has been shown to be simple, reproducible, fast, and free of solvent-related toxicity issues. The formed emulsion is transiently stabilised by the high viscosity of the external phase (provided by PVA) rather than by interfacial phenomena during this method, which is why it is known as the "quasi-emulsion method." The method is based on the rate of diffusion of organic solvent (from the internal/organic phase) and water (from the external phase) in opposite directions. When the organic phase, which contains drug and polymer in dissolved form, is mixed with the aqueous phase, which contains surfactant, the interfacial tension between the organic and aqueous phases increases. Because the attraction forces between the drug and the organic solvent are greater than those between the organic solvent and water, the organic solvent begins to disperse as unstable droplets in the aqueous phase, resulting in a quasi-emulsion system. The dissolved PVA increases the viscosity of the aqueous phase, providing the system with transient stability. Because the organic solvent has been transiently stabilised, it begins to diffuse towards the aqueous phase, reducing the solubility of the dissolved polymer. Meanwhile, counter diffusion of water in the emulsion droplet increases the viscosity of the organic phase as the dissolved polymer begins to solidify due to its low solubility in water. Continuous diffusion of organic solvent outside the droplet and counter diffusion of aqueous phase inside the droplet results in polymer states shifting as follows. : *Solution state →gel state→ glassy state.* In its glass state, the polymer forms a porous shell that encloses the drug and organic solvent. Further counter-diffusion of organic solvent and water through the porous shell results in drug precipitation inside the shell and the formation of interconnected pores on the shell's surface. Finally, the polymer solidifies, forming porous, interconnected pores around the crystallized/amorphous drug.(5, 11)

Table 4
Displays the results of the various evaluation tests performed on design batches

	Dependent Variable (Response)				
Batch code	Y1 Particle Size (µm)	Y2 Entrapment efficiency (%)	Y3 Production yield (%)	Y4 Loading Efficiency (%)	Y5 Amount of Vitro drug release at 60min
B 1	600.75	99.32	94.45	80.12	86.33
B 2	498.87	96.2	85.59	70.45	79.12
B 3	498.87	96.2	85.59	70.45	79.12
B 4	520.78	97.25	81.36	69.89	80.25
B 5	512.89	97.14	83.25	68.45	80
B 6	498.87	96.2	84.45	67.98	79.12
B 7	589.47	98.01	93.24	80.02	83.23
B 8	471.26	94.55	82.54	69.69	78.12
B 9	545.87	97.59	90.45	76.56	81.12

B 10	432.89	93.59	81.56	69.44	77.05
B 11	390.56	91.12	75.69	61.89	74.56
B 12	400.012	92.52	73.45	59.86	75.85
B 13	350.12	90.35	72.56	60.56	73.45
B 14	570.85	98	87.56	72.76	82.56
B 15	375.45	91.25	67.25	55.45	70.45

Confirmed that the model was significant and independent variables of the model had significant effect on repose variables. Response surface plots were generated to graphically represent the effect of independent variables on response variables. The contour plot 3-D response surface plot for various response variables are given in Figs.13, 14, 15, 16, 17. The equation for all the responses is mentioned below the interaction plots.

Particle Size

The size of the prepared microsponges ranged between 350.12 μm and 600.75 μm. The regression analysis proved a signifcant effect of homogenization speed and drug/polymer ratio on the size of microsponges. No interaction term had a signifcant effect on the size of prepared microsponges. A negative linear relationship was observed between homogenization speed and size of microsponges. This means that the size of microsponges decreased as the homogenization speed increased. This was possibly because, at higher stirring speed, the dispersion system experienced a vigorous and high mechanical shear force, resulted in the rapid dispersion of organic phase globules. The homogenization speed also possibly prevented the coalescing of small dispersed globules into large droplets. This observation was in line with the results previously reported by Jelvehgari et al.(12), who also observed a decreased in microsponges size upon increasing the homogenization speed. The model F –value 8.07 & p –value 0.0232 implies the model is significant. The predicted R^2 of 0.9594 is in reasonable agreement with the Adjusted R^2 of 0.9929 and difference is less than 0.2.

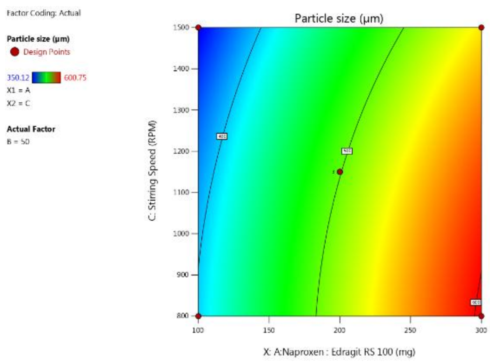

Fig 13. (a) Contour plot depicting the effect of stirring Speed and drug/polymer ratio on particle size

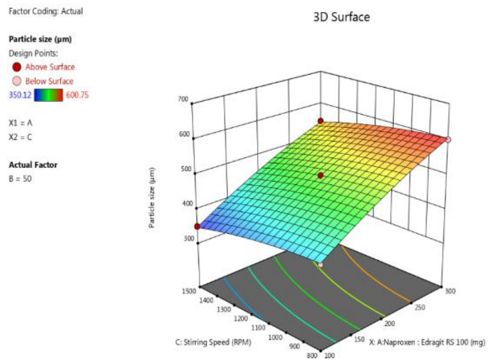

Fig 13. (b) Three-dimensional surface plot depicting the effect of stirring speed and drug/polymer ratio on particle size

Particle size (Y1) $= 498.87 + 98.85X1 - 3.37 X2 - 29.29X3 + 8.43X1X2 - 1.25X1X3 - 11.56X2X3 - 13.78X1^{2} - 3.51 X2^{2} - 10.90X3^{2}$.

% Entrapment Efficiency

The % entrapment efficiency of designed batches was between 90.35 and 99.32 %. Batch B1 had the highest efficiency of 99.32 % whereas batch B13 had the lowest efficiency of 54.02%. Among all independent variables, drug/ polymer ratio and amount of PVA had a signifcant effect on the drug entrapment efficiency. The result of regression analysis suggested a negative effect of PVA concentration on entrapment efficiency of microsponges whereas drug/polymer ratio had a positive effect. High the amount of PVA in the external phase increased the solubility of the drug in water so possibly more amount of drug was able to diffuse from the microsponges to the aqueous phase and thus decreased the entrapment efficiency of microsponges.
The model F –value 10.73 & p –value 0.0128implies the model is significant. The predicted R^2 of 0.8844 is in reasonable agreement with the Adjusted R^2 of 0.9798.

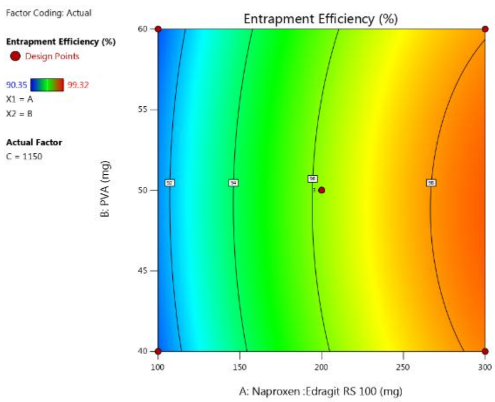

Fig 14. a) Contour plot depicting the effect of PVA concentration and drug/polymer ratio on % entrapment efficiency

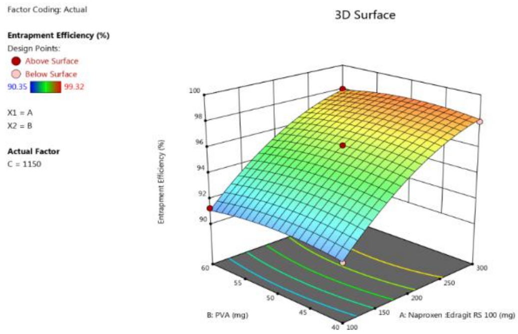

Fig 14. b) Three-dimensional surface plot depicting the effect of PVA concentration and drug: polymer ratio on % entrapment efficiency

% Entrapment efficiency (Y2) = 96.20 + 3.46X1 - 0.088X2- 1.27X3 - 0.0300X1X2 + 0.1100X1X3 -0.2675X2X3-1.15X1^2-0.4587X2^2-0.1088X3^2

Production Yield

The % product yield of designed batches ranged between 67.25 and 94.45% .The regression analysis proved a signifcant effect of all the independent variables on the % product yield. Among all independent variables, the drug/polymer ratio had the highest impact on % product yield followed by homogenization speed and amount of PVA (Fig. 3). The high drug/polymer ratio possibly decreased the diffusion rate of the internal organic phase to external aqueous by providing high viscosity. The slow diffusion provided more time for droplet formation and polymer solidification thus increased the % product yield. The model F –value 15.84 & p –value 0.0055 implies the model is significant. The predicted R^2 of 0.9493 is in reasonable agreement with the Adjusted R^2 of 0.9891

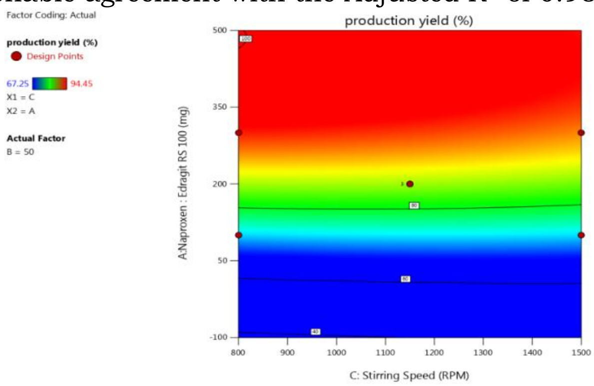

Fig 15. (a) Contour plot depicting the effect of stirring speed and drug/polymer ratio on % production yield

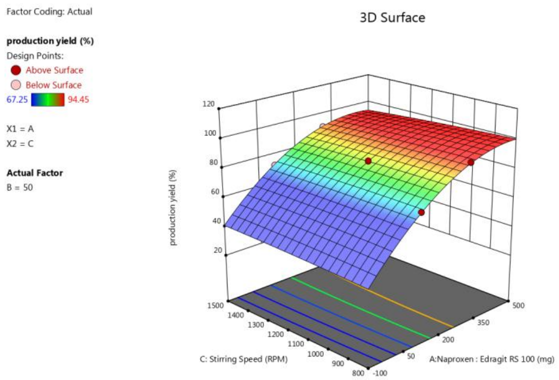

Fig 15. b) Three-dimensional surface plot depicting effect of stirring speed and drug: polymer ratio on % production yield

% Yield–Y3 = 85.10 + 9.59X1 – 0.7038X2 – 0.6750X3 +3.53X1X2-0.7775X1X3 +0.2275 X2X3 – 1.81X1^2 -2.36 X2^2 – 0.5650X3^2

DesirabilityFunction Index

Multiple responses optimization to given experimental factors applying RSM is often unsatisfactory, because what is optimal for one response may not be optimal for other responses. There are several methods to find the best compromise among multiple responses. Derringer's desirability function is the most popular methodology, which searches for a combination of factor levels that simultaneously satisfies the requirements for each response in the design.(13)

Table 5
Estimated desirability values

Expt. No	Particle size (µm)	Entrapment Efficiency (%)	Production yield	Individual desirability			(CD)	Rank
				Particle size	Entrapment Efficiency	Production yield		
B1	600.75	99.32	94.45	1	1	1	1	1
B2	498.87	96.2	85.59	0.593504	0.652174	0.674265	0.639057	7
B3	498.87	96.2	85.59	0.593504	0.652174	0.674265	0.639057	7
B4	520.78	97.25	81.36	0.680924	0.769231	0.51875	0.647696	6
B5	512.89	97.14	83.25	0.680924	0.756968	0.588235	0.661287	5
B6	498.87	96.2	84.45	0.593504	0.652174	0.674265	0.639057	7
B7	589.47	98.01	93.24	0.954993	0.853958	0.955515	0.920219	2
B8	471.26	94.55	8254	0.483342	0.468227	0.562132	0.502941	8
B9	545.87	97.59	90.45	0.781032	0.807135	0.526103	0.692195	4
B10	432.89	93.59	81.56	0.330248	0.361204	0.526103	0.397394	9
B11	390.56	91.12	75.69	0.161353	0.085842	0.310294	0.162586	11
B12	400.01	92.52	73.45	0.199066	0.241918	0.227941	0.222244	10
B13	350.12	90.35	72.56	0	0	0.195221	0	12
B14	570.85	98	87.56	0.880701	0.852843	0.746691	0.824669	3

B15	375.45	91.25	67.25	0.101065	0.100334	0	0	12

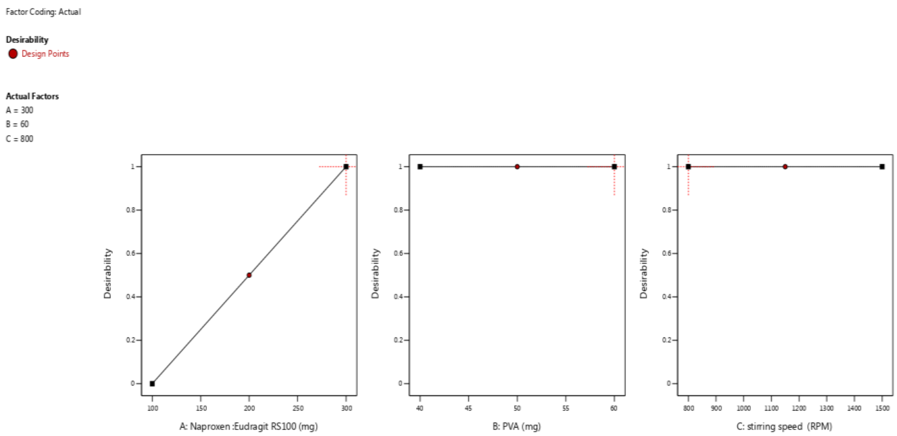

Fig 16. Individual response desirability index of all independent variables

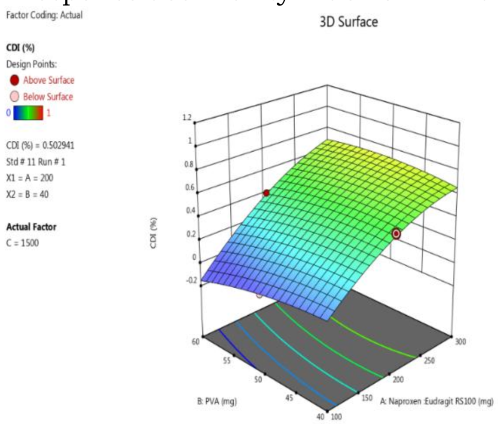

Fig 17. a) Three -dimensional surface pot depicting effect of PVA concentration and drug: polymer ratio on Composite desirability index

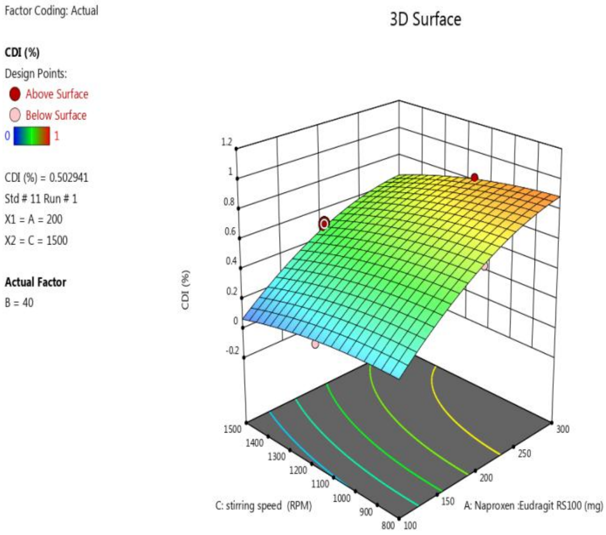

Fig 17. b) Three-dimensional surface plot depicting effect of stirring speed and drug: polymer ratio on Composite desirability index

Pre compression Data

Batch	Angle of repose	Bulk density	Tapped density	Hausner Ratio	Compressibility %
B1	26.08	0.71	0.76	1.07	7.04

Post compression Data (Tablet evaluation parameter)

NON –OFFICIAL TESTS					OFFICIAL TESTS		
Formulation	Hardness (kg /cm $^{2)}$	Friability (%w/w)	Thickness (mm)	Diameter (mm)	Weight Variation (mg)	Drug content (%)	Disintegration time (min)
Core tablet	3.91	0.51	3.24	10.11	349.3(94 %)	97.02	30 min
Coated tablet	4.46	0.54	4.50	12.50	365.32	-	-

In vitro dissolution Study

Media	Time (hrs)	Cumulative % drug release
pH 1.2	0	0
	1	0.20
	2	2.88
pH 6.8	3	7.36
	4	11.97
	5	12.54
pH 7.4	6	18.57
	7	20.55

	8	29.27
	9	40.11
	10	51.09
	11	62.22
	12	73.62
	13	85.46
	14	97.43

Kinetic Data Analysis

The drug release data of optimized Batch were fitted into different kinetic models which show that the drug release from tablet formulations follows korsmeyer - Peppas release.

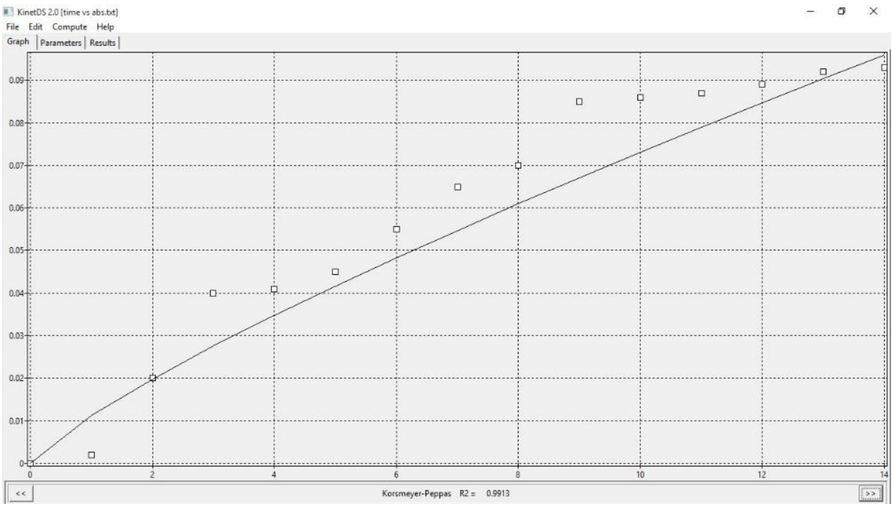

Fig 18. Drug Release by Korsemeyer -Peppas

Conclusion

It could be concluded that application of experimental design is helpful tool for the development of microsponges of naproxen by emulsion solvent diffusion technique using RS 100 as a polymer for enhancement of solubility ,flow properties & and compression characteristics and controlling the release rate up to 5 hrs. The optimized batch B1 MS formulation obtained from DFI with particle size of 600.75 µm, entrapment efficiency 99.32% & production yield 94.45 % .The prepared optimized Microsponge formulation was then formulated into tablet to get controlled release of drug up to 14 hrs. Drug release kinetics of this formulation correspond best to Korsmeyer & Peppas release model and drug release mechanism as per n value of Korsmeyer & Peppas was found to be 0.94 indicates Non- Fickian zero-order release.

Acknowledgement

The authors are very much thankful to the Sanjivani College of Pharmaceutical Education and Research for providing necessary suitable lab facilities to carry out this work. The results described in this paper are a part of academic thesis.

Abbreviation

MS – microsponge
QESD -Quasi Emulsion Diffusion method.
PVA - Polyvinyl alcohol**.**
FTIR **–**Fourier transform infrared spectroscopy
DSC **-** Differential scanning calorimetry
DFI – Desirability function Index
CD – Composite desirability.

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