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Formulation and Evaluation of Flurbiprofen Microsponges Tablet for Effective Treatment of Rheumatoid Arthritis.

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KEYWORDS
Flurbiprofen; microsponge; box-behnken design.

ABSTRACT:

Introduction: Rheumatoid arthritis (RA) is a chronic, autoimmune and inflammatory disease that mostly impacts the joints. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. Flurbiprofen is a non-steroidal anti-inflammatory drug, indicated for the relief of inflammation.

Objectives: The aim of the present study was to develop & optimize the microsponges based of Flurbiprofen tablet for Chronotherapeutics for enhanced therapeutic effect.

Methods: 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 like concentration of PVA (X1), Volume of Dichloromethane (X2) & stirring speed (X3) on the Entrapment Efficiency (Y1), Mean particle size (Y2) and Drug release at 8 hr (Y3) using box behnken design. The optimized formulation was subjected to in vitro study. Morphology of obtained microsponges was revealed by scanning electron microscope.

Result: The F7 was selected as optimized formulation based on particle size of 42.81µm, entrapment efficiency of 88.19%, and drug release at 8 h 64.94%.

Conclusion: The results showed that, as stirring speed increases, the particle size decreases and entrapment efficiency increases. While volume of dichloromethane increases, particle size decreases. Morphology was found to be porous and spherical. Optimized batch of Flurbiprofen microsponge was further formulated as tablet formulation.

1. Introduction

A polymeric system made up of porous microspheres is called the Microsponge Delivery System (MDS). Their small, spherical, sponge-like particles are made up of several interconnected gaps inside a non-collapsible structure that has a large porous surface area that allows the regulated release of the active component. By capturing the less water-soluble medications in its pores, the microsponge system in oral drug delivery accelerates their solubilization. The medicine is effectively reduced to microscopic particles due to the extremely small pores, and the substantial increase in surface area accelerates the solubilization process. Rheumatoid arthritis is a chronic inflammatory systemic disease, mainly characterized by synovitis of small joints, especially of hands and feet. Persistent synovitis leads to pain, joint swelling, stiffness, decreased mobility and

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joint space narrowing; synovial hyperplasia causes erosions and joint deformities. (1,2.3)

The biological and physiological processes of the brain and body depend heavily on circadian rhythms. Chronobiology plays a crucial part in rheumatoid arthritis (RA), where major symptoms including stiffness and pain in the joints are most noticeable in the morning. These symptoms may be mediated by circadian cycles of hormone and cytokine levels. According to chronobiological principles, the best outcomes may come from chronotherapy, which synchronises treatment schedules with each patient's unique circadian rhythm. Studies on patients with RA who received Flurbiprofen or NSAID. chronotherapy indicate that this strategy can enhance results and lessen side effects. One method to solve such problems is to find dosage form capable of releasing the drug such as Chronotherapeutical modified release microsponge tablets. (4)

Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. Flurbiprofen is a non-steroidal anti-inflammatory drug, indicated for the relief of inflammation.(5)

Flurbiprofen is an important analgesic and non-steroidal anti-inflammatory drug (NSAID) also with anti-pyretic properties whose mechanism of action is the inhibition of prostaglandin synthesis. Flurbiprofen is rapidly eliminated from the blood, its plasma elimination half-life is 3-6 hours and in order to maintain therapeutic plasma levels. (6)

2. Objectives

The aim of the research work was to design microsponges for chronotherapeutic drug delivery system to improve efficacy of a drug.

Some drugs produce gastric irritation in stomach. Some drugs produce unwanted systemic side effects like increasec risk of blood clot, Oedema, heart burn, enzymatic degradation of drug in small intestine. Formulating these drugs as microsponges can address these problems effectively.

Microsponges can be designed to work as chronotherpeutic drug delivery system where durg release can be programmed in synchronization with circadian cycle of the body and disease condition like rheumatoid arthritis. This can effectively make drug available to have better monitoring of drug concentration in the body.

Material and Methods

Material:

Flurbiprofen powder was supplied by Vetina Healthcare, Pune, Eudragit polymers (RS-100) powder were obtained from Evonik, Mumbai, polyvinyl alcohol (PVA) from Loba chemie, India. All other materials used in this study were of analytical grade.

Method:

Flurbiprofen loaded microsponge preparation:

Flurbiprofen microsponge preparation: By using a quasi-emulsion solvent diffusion method, the microsponges containing Flurbiprofen were made. An internal phase was added, consisting of 1% triethylcitrate (TEC) and Eudragit RS-100 dissolved in dichloromethane, to increase the polymer's plasticity. Flurbiprofen 100 mg was then added and dissolved at 35°C using ultrasonication. Following that, the mixture was added to 100 millilitres of polyvinyl alcohol aqueous solution, which was used as the external phase. The combination was stirred for two hours at 500, 1000, and 1500 revolutions per minute. As a result of dichloromethane evaporating out of the system, microsponges were created. To ascertain the manufacturing yield, the microsponges underwent a 12-hour drying process at 40°C after being cleaned with water, filtered, and kept for later study. (7,8)

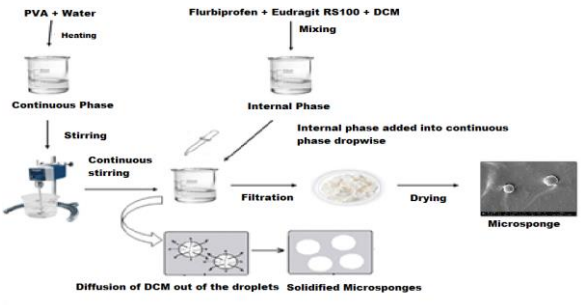

Fig 1: Formulation of microsponge by QESD

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

Preliminary trial batches were taken for selection of polymers like Eudragit RS 100, Eudragit RL100 and Ethyl cellulose. Eudragit RL100 and ethyl cellulose were not used to manufacture spherical, stiff microsponges. Eudragit RS 100 produced the necessary micrometer-sized microsponges that were spherical and stiff. Eudragit RS 100 was therefore utilised as a polymer for additional research.

Table 1: Drug Polymer Ratio Selection

Formulation code	Drug:polymer ratio (mg)	Entrapment efficiency (%)	Mean particle size (µm)
FLBA	2:1	67.67±0.66	24.81±3.45
FLBB	1.5:1	83.84±1.65	42.87±2.73
FLBC	1:1	77.8±2.05	38.07±3.80
FLBD	1:1.5	70.5±3.00	35.89±4.47

Table 2: Independent variables

Factors	Actual Value			Levels used (Coded Value)		
	Low	Medium	High	Low	Medium	High
Concentration of PVA	400	500	600	-1	0	+1
Volume of DCM	5	10	15	-1	0	+1
Stirring Speed	500	1000	1500	-1	0	+1

3D Response Surface Plots & Contour plot

The possible correlation between three variables examined by 3D wireframe and surface plots.

Desirability Criteria

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

Optimization

Entrapment Efficiency

Flurbiprofen loaded microsponges theoretically equivalent to 100 mg of Flurbiprofen were weighed, crushed and extracted with 5 ml of methanol by vortexing. After the sample had been appropriately diluted with methanol, it was centrifuged for 10 minutes at 2000 rpm, filtered, and subjected to spectrophotometric analysis at 247 nm. The effectiveness of entrapment was calculated using a formula. (9)

Drug Encapsulation efficiency = (Actual Drug Content/ Theoretical Drug Content) X100

Particle size analysis

Optical microscopy was used to measure particle size of microsponge by using digital microscope (Motic CV5-2), calibrated with ocular micrometer (AmScope MR400 Microscope calibration slide). A small amount of the water-dispersed selected microsponge formulation was put on a glass slide in the shape of droplets. Through the use of a digital microscope, the dispersion drop was examined. 300 particle sizes were averaged, and the result was computed. (10)

Table 3: Experimental runs suggested by the Box Behnken design

Run	Independent Variable		
	X1 Conc of PVA(mg)	X2 DCM (mg)	X3 StirringSpeed (rpm)
B1	500	5	500
B2	500	10	1000
B3	400	10	500
B4	400	10	1500
B5	600	10	500
B6	500	10	1000
B7	400	15	1000
B8	500	15	500
B9	600	5	1000
B10	600	10	1500
B11	500	10	1000
B12	500	10	1000
B13	400	5	1000
B14	500	10	1000
B15	500	5	1500
B16	500	15	1500
B17	600	15	1000

In Vitro Drug Release Study at 8 hr

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

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100 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 L max 247 nm using UV- Visible spectrophotometer. The cumulative percentage of drug release is calculated using an equation obtained from a standard curve. (11)

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 entrapment efficiency, particle size, drug release at 8 hr. The optimized formulation was selected on the basis of particle size & high entrapment efficiency & drug release at 8 hr 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. Drug-excipient interactions are likely to be detected by DSC, which also aids in evaluating the sample's crystalline or amorphous physical characteristics. Thermal analysis was conducted on a physical mixture consisting of flurbiprofen and Eudragit RS 100.

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 3,4,5 contain FTIR of drug & microsponge.(12)

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 microsponge was obtained. Thermogram were recorded using lab solution software. Fig no 5 & 6 contain DSC of drug & Microsponge.(13)

Surface morphology

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. Fig No 7&8 contain SEM of Flurbiprofen.

Colon specific tablet

Preparation of colon specific tablet

Specific weight of selected prepared microsponges equivalent to 250 mg of Flurbiprofen. 1% magnesium stearate as a lubricant, and, starch, MCC, lactose was mixed well using mortar and pestle for 15 min, then undergo physical evaluation before compression. The powder combinations' compressibility, bulk density, tapped density, and angle of repose were assessed prior to the creation of tablets. (14)

Table 4: Composition of colon targeted tablet of Flurbiprofen

Ingredient (mg)	Quantity (mg)	Category of Excipient
Microsponge	110	Act as API
Starch	23	Diluent
MCC	70	Binder
Directly compressible lactose	5	Excellent compressibility properties.
Magnesium stearate	2	Lubricant

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Preparation of coating solution

The Flurbiprofen 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.(15)

Evaluation of Tablet

Pre compression Evaluation:

1. Angle of repose:

The angle of repose of microsponge was determined by the funnel method. tanθ = h/r; Where θ = angle of repose, h = height, and r = radius.

2. 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.

3. 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 poorflowability.

4. Carr's index

It indicates powder flow properties. It is expressed in percentage and is given by I = (Dt – Db) × 100, Where Dt is the tapped density of the powder and Db is the bulk density ofthe powder. (16)

Post compression Evaluation:

1. Hardness:

The hardness at which the tablet crushes is the hardness of thetablet. Hardness of the 3 tablets from each batch was measured using Monsanto hardness tester. Generally Maximum 5 k/sq. in Hardness is required.

2. Friability

Roche friabilator is used to evaluate the ability of the tablet to withstandabrasion. The Roche friabilator is used to test a tablet's friability, which determines whether or not the tablet is stable against abrasion. This is composed of a machine that rotates a plastic drum at 25 revolutions per minute for 100 revolutions. The twenty tablets that were weighed before the test are then removed of the drum, wiped with a cloth, and weighed again; for a standard tablet, the weight difference cannot be less than 0.5 to 1.0%. F = (W1–W2)/W1×100.

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

3. Thickness and Diameter

The thickness of individual tablets is measured with a micrometer, which gives us information about the variation between tablets. Tablet thickness should be within a ±5% variation of a standard value. Tablet Thickness and diameter were accurately measured by using digital vernier caliper in mm.

4. Weight variation

Twenty tablets were individually weighed for the USP weight variation test. The average weight of each tablet was then calculated, and the weight of each tablet was compared to the average weight variation tolerance. (17,18)

5. 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 247 nm. (20)

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Table 4: 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	$Q0^{1/3} - Qt^{1/3} = KHC\ t$
5	Korsmeyer-peppas equation	$Mt / Ma = K\ tn$

6. Kinetic data analysis

Examine the data on in vitro release. The release kinetics were described using a variety of kinetic models. Systems in which the drug release rate is independent of concentration are described by the zero order. The release from a system where the release rate depends on concentration is described in the first order. Based on Fickian diffusion, Higuchi defined the release of pharmaceuticals from an insoluble matrix as the square root of a time-dependent process. 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).(21)

Results & Discussion:

Mechanism of forming microsponges

It has been demonstrated that the quasi-emulsion technique for creating microsponges is easy to use, rapid, reproducible, and free of toxicity concerns associated with solvents. Because the high viscosity of the external phase (supplied by PVA) temporarily stabilises the generated emulsion instead of interfacial phenomena during this procedure, it is referred to as the "quasi-emulsion method." The technique is based on the rate at which water (from the exterior phase) and organic solvent (from the internal/organic phase) diffuse in opposing directions. The organic phase's interfacial tension rises when it is combined with the surfactant-containing aqueous phase, which contains the medicine and polymer in dissolved form. 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 system gains temporary stability from the increased aqueous phase viscosity caused by the dissolved PVA. The solubility of the dissolved polymer is decreased as a result of the organic solvent diffusing towards the aqueous phase due to its temporary stabilisation. Given the dissolved polymer's low solubility in water, counter diffusion of water in the emulsion droplet causes the organic phase's viscosity to increase as the polymer starts to solidify. 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.

Experimental Design:

Displays the results of the various evaluation tests performed on design batches Confirmed that the model was significant and independent variables of the model had significant effect on repose variables. The impact of independent factors on response variables, response surface plots were created. For a range of response variables, the contour plot 3-D response surface plot are given in Figs.12,13,14. The equation for all the responses is mentioned below the interaction plots.

% Entrapment Efficiency

The % entrapment efficiency of designed batches was between 74.25 and 88.78%. Batch B4 had the highest efficiency of 88.78 % whereas batch B1 had the lowest efficiency of 74.25%. Among all independent variables, amount of PVA and stirring speed had a significant effect on the

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drug entrapment efficiency. Regression analysis results indicated that stirring speed had a favorable impact on microsponges' entrapment efficiency, whereas PVA concentration had a negative 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.

a decrease in mean particle size. The particle size was found to be inversely proportional to the stirring rate. At higher stirring rate, a vigorous, uniform, increased mechanical shear was imposed and this resulted in a rapid division of the formed droplets, which might have less chance of coalescing into bigger droplets as shown in fig. 10. This led to decrease in particle size with increasing stirring rate.

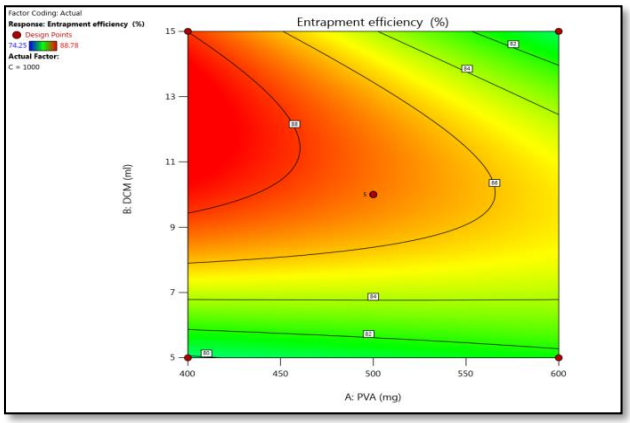

Fig 9. a) Contour plot depicting the effect of Dichloromethane and PVA concentration on % entrapment efficiency

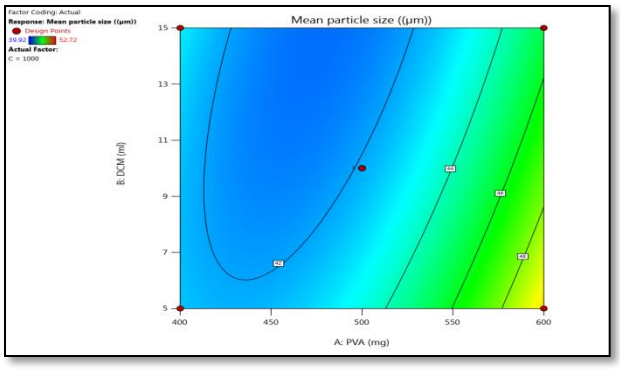

Fig 10. (b) Contour plot depicting the effect of Concentration of Dichoromethane and PVA concentration on Mean Particle size

Mean Particle size

The particle size was found to be inversely proportional to quantity of internal phase (DCM). The negative relationship between internal phase volume and mean particle size showed that microsponges' particle sizes reduced as internal phase volume increased. Particle sizes of microsponges can be directly attributed to apparent viscosity of internal phase. The globules of the produced emulsion could readily split into smaller droplets when the internal phase with lower viscosity was poured into the continuous phase, resulting in a decrease in mean particle size. The particle size was found to be inversely proportional to the stirring rate. At higher stirring rate, a vigorous, uniform, increased mechanical shear was imposed and this resulted in a rapid division of the formed droplets, which might have less chance of coalescing into bigger droplets as shown in fig. 10. This led to decrease in particle size with increasing stirring rate.

Drug release at 8 hr

The particle size was found to be inversely proportional to quantity of internal phase (DCM). The negative influence of internal phase volume on mean particle size indicated that increasing the internal phase volume decreased the particle size of microsponges. Particle sizes of microsponges can be directly attributed to apparent viscosity of internal phase. When the internal phase with lower viscosity was poured into continuous phase, the globules of the formed emulsion could easily divide into smaller droplets and mean particle size decreases. The particle size was found to be inversely proportional to the stirring rate. At higher stirring rate, a vigorous, uniform, increased mechanical shear was imposed and this resulted in a rapid division of the formed droplets, which might have less chance of coalescing into bigger droplets as shown in fig. 11. This led to decrease in particle size with increasing stirring rate. As particle size reduced drug release rate increases due to available surface area.

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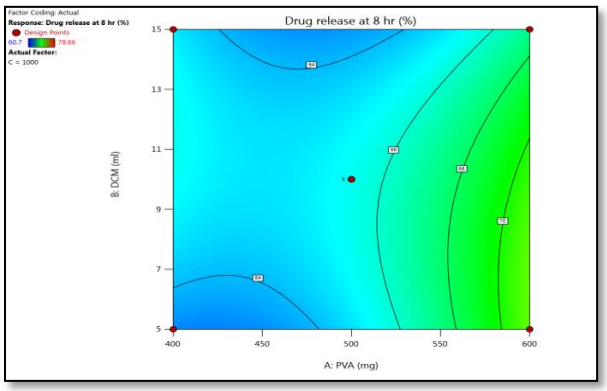

Fig 11. c) Contour plot depicting the effect of Dichloromethane and PVA concentration on Drug release at 8 hr

Desirability Function 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.

Table 5: Estimated desirability values

		Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3
Std	Run	A:PVA (Mg)	B: DCM (ml)	C:Stirring speed (Rpm)	Entrapment efficiency (%)	Mean particle size (µm)	Drug release at 8 hr %
9	1	500	5	500	74.25± 2.36	50.24±1.55	66.25±1.72
17	2	500	10	1000	86.56±1.42	42.63±1.82	65.74±0.37
5	3	400	10	500	84.74±0.66	45.85±1.93	68.63±1.62
7	4	400	10	1500	88.78±2.56	42.44±2.43	73.49±0.45
6	5	600	10	500	82.82±2.18	52.72±0.44	60.70±1.61
15	6	500	10	1000	87.77±1.73	40.5±1.72	65.24±0.88
3	**7**	**400**	**15**	**1000**	**88.19**±1.09	**42.81**±0.72	**64.94**±0.52
10	8	500	15	500	83.93±0.77	45.33±1.84	65.28±1.55
2	9	600	5	1000	81.34±2.56	50.17±1.77	71.32±1.88
8	10	600	10	1500	85.64±3.12	45.43±1.39	69.16±2.27
16	11	500	10	1000	85.5±2.76	42.66±1.06	65.82±2.48
14	12	500	10	1000	87.63±0.69	42.12±1.11	65.26±1.63
1	13	400	5	1000	80.17±1.83	42.55±2.53	63.63±1.73
13	14	500	10	1000	87.66±1.48	42.58±2.84	65.15±1.84
11	15	500	5	1500	84.08±1.33	39.92±1.38	78.66±0.63
12	16	500	15	1500	81.4±2.47	41.38±1.41	67.34±2.36
4	17	600	15	1000	79.8±2.73	45.26±2.60	66.64±0.55

% Entrapment efficiency:

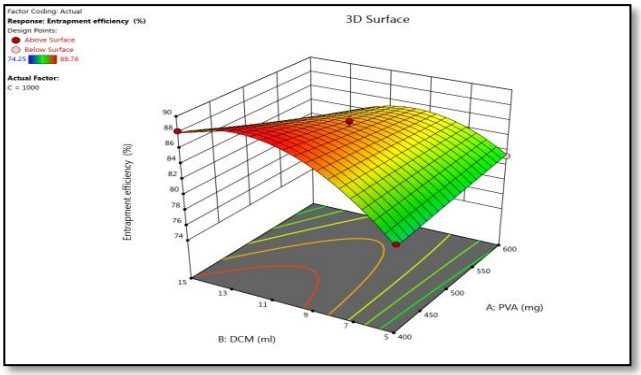

Fig 12. a) Three-dimensional surface plot depicting effect of Dichoromethane and PVA concentration on % entrapment efficiency

% Entrapment efficiency (Y1) = +87.02 - 1.53X1 + 1-69X2 + 1.77X3 – 2.39X1X2- 0.305X1X3 - 3.09X2X3- $0.034X1^2$- $4.61X2^2$- $1.49X3^2$

Mean particle size (Y2)

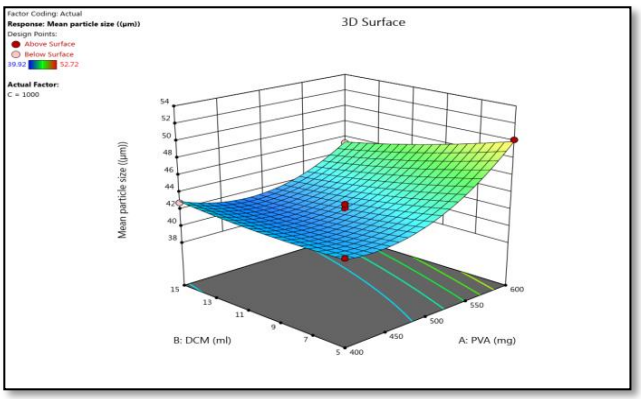

Fig 13. b) Three-dimensional surface plot depicting effect of volume of Dichloromethane & concentration of PVA on Mean particle size

Mean particle size (Y2) = 42.10 + 2.49X1 – 1.01X2 – 3.12X3 –1.29X1X2–0.97X1X3 +1.59 X2X3 – $2.75X1^2$ +0.353 $X2^2$ + $1.77X3^2$

Drug release at 8 hr

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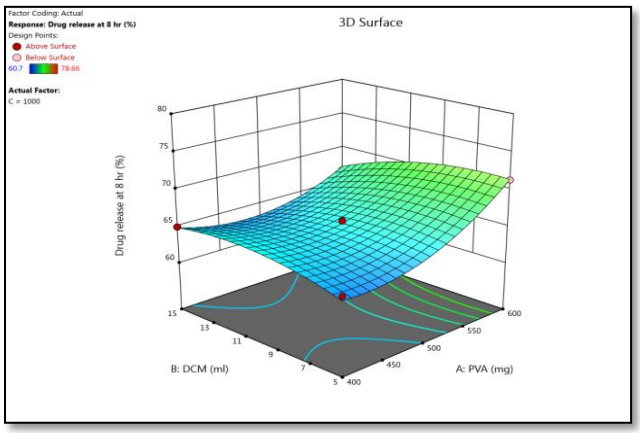

Fig 14. c) Three-dimensional surface plot depicting effect of Dichoromethane and PVA concentration on drug release at 8 hr

Drug release at 8 hr $(Y3) = 65.44 + 2.66X1 – 0.617X2 – 3.47X3 – 1.50X1X2–0.1100X1X3–0.2675X2X3–1.15X1^2–0.4587X2^2–0.1088X3^2$

Drug & excipient compatibilityFTIR

FTIR show the IR spectra of Flurbiprofen 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 Flurbiprofen in the physical mixture.

TABLE 4: FTIR ranges

Sr. no	Functional Group	Ranges (cm $^{-1}$)
1	C = O (carboxyl group)	1697.41
2	C–O	1219.05
3	-CH3 bend	1442.00
4	O–H (carboxylic acid	3009.05

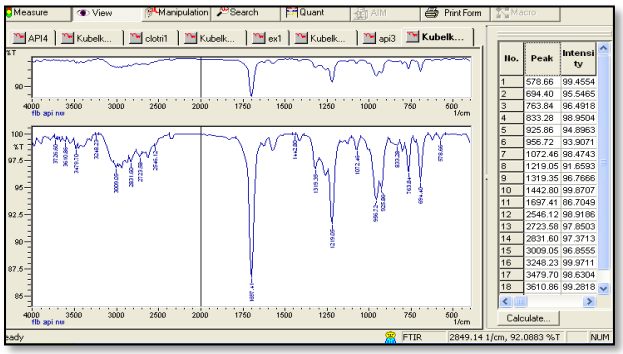

Fig 2. FTIR of Flurbiprofen

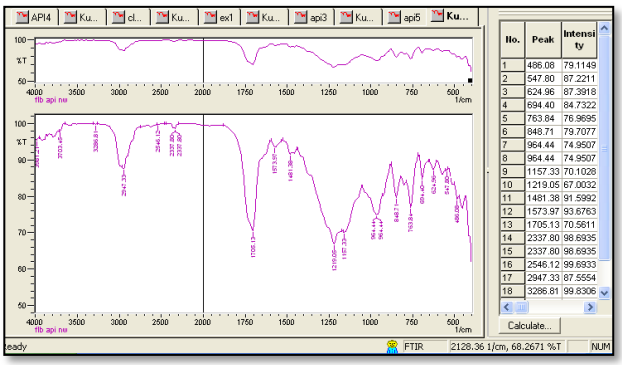

Fig 3. FTIR of drug & polymeric mixture

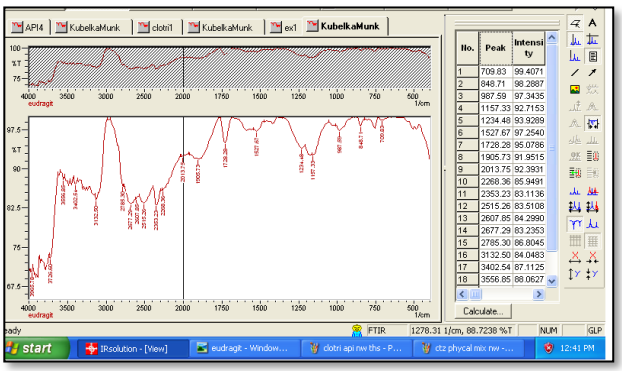

Fig 4. FTIR of Microsponge

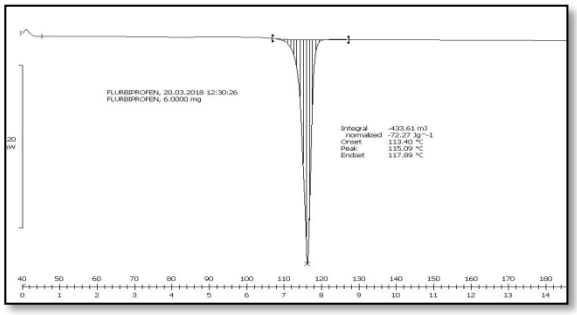

Fig 5. DSC of Flurbiprofen

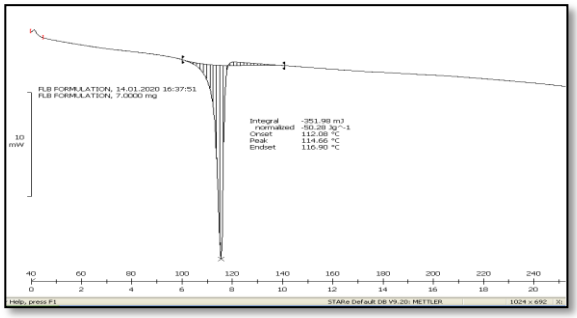

Fig 6. DSC of Flurbiprofen Microsponge

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Scanning Electron Microscopy

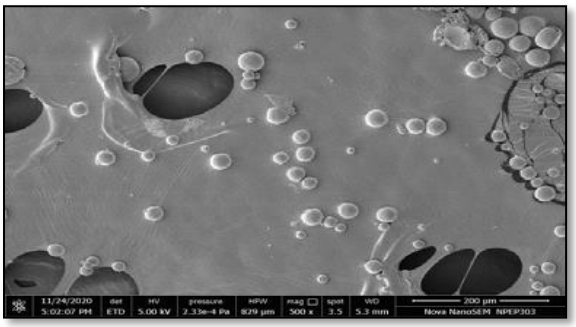

Fig 7. SEM of selected microsponge (Magnification x500)

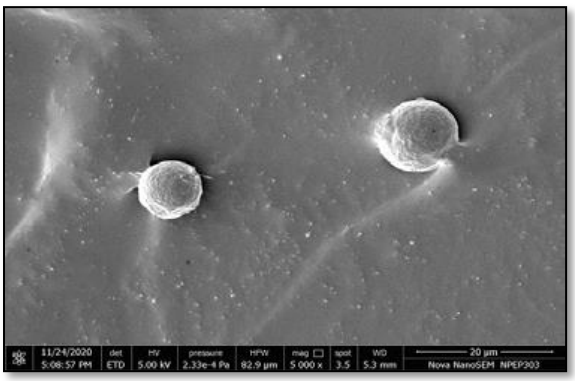

Fig 8. SEM of selected microsponge (Magnification x5000)

Thermal analysis by Differential scanning calorimetry

DSC of the Flurbiprofen, & Flurbiprofen 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. 5& 6.

TABLE 6: Pre compression Data

Batch	Angle	Bulk density	Tapped density	Hausner Ratio	Compressibility %
B7	28.12	0.73	0.77	1.05	5.19

TABLE 7: Post compression Data

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	3.41	0.63	3.84	7.05	203.3 (97%)	97.02	12 min
Coated tablet	4.46	0.34	4.12	8.50	365.32	-	-

TABLE 8: In vitro dissolution Study

Media	Time (hrs)	Cumulative % drug release
pH 1.2		0
	1	0.20±0.4
	2	0.88±0.12
pH 6.8	3	1.36±0.22
	4	3.97±0.37
	5	4.54±0.70
pH 7.4	6	18.57±1.07
	7	22.55±2.26
	8	29.27±1.66
	9	36.11±2.13
	10	43.09±1.88
	11	50.22±2.36
	12	57.62±1.66
	13	64.86±1.61
	14	71.33±2.84
	15	78.12±1.63
	16	86.25±2.95
	17	93.50±1.72
	18	97.45±2.74

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.

Conclusion:

It could be concluded that application of experimental design is helpful tool for the development of microsponges of Flurbiprofen 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 18 hrs. The optimized batch B7 MS formulation obtained from DFI with particle size of 42.81 µm, entrapment efficiency 88.32% & drug release at 8 hr 64.94 %

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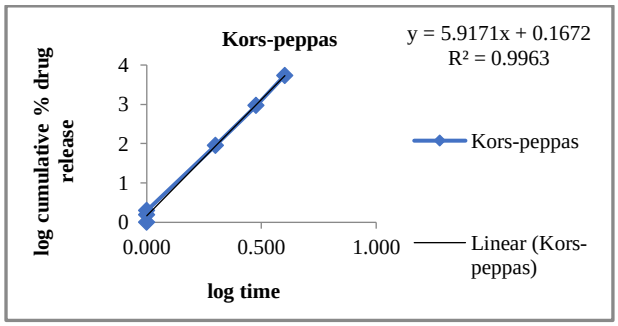

Fig 5. Drug Release by Korsemeyer–Peppas

The prepared optimized Microsponge formulation was then formulated into tablet to get controlled release of drug up to 18 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 0.996 indicates Non- Fickian zero-order release.

Acknowledgement

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Abbreviation

MS- microsponge; QESD- Quasi Emulsion Diffusion method; DSC- Differential scanning calorimetry; DFI- Desirability function Index ; CD- Composite desirability.

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