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Formulation Development and Evaluation of Febuxostat Loaded Microsponges

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Abstract: The objective of the present investigation was to improve dissolution characteristics of febuxostat, a BCS class-II drug by using microsponge drug delivery system. Febuxostat loaded microsponges prepared by using quasi emulsion solvent diffusion method. Optimized formulation was characterized by fourier transform infrared spectroscopy (FTIR), differential scanning calorimeter (DSC). Microsponge are design to deliver a pharmaceutical active ingredient efficiently at minimum dose and also to enhance stability, flexibility in formulation, reduce side effect and modify release profile. In-vitro dissolution profile was compared with the marketed product. Febuxostat loaded microsponges are promising approach for the controlled release drug delivery for Febuxostat and can be used for the development of suitable solid dosage form for commercialization. In-vitro dissolution results revealed that microsponge formulation containing 11:1 drug:polymer ratio has shown controlled release i.e. 97.31% up to 12 hrs which indicated that microsponges has shown better controlled release of drug, due to microporous nature of polymer generated in which the drug was entrapped. The microsponges drug delivery system formulated for the longer treatment of gout with hyperuricemia with increase stability.

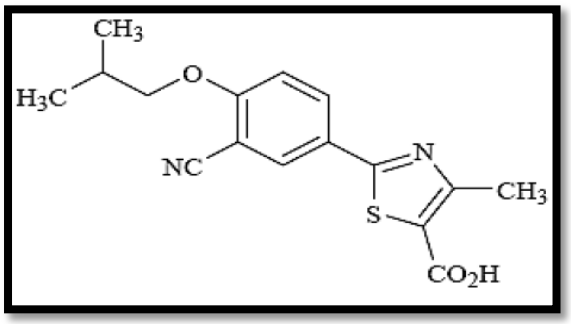
Keywords: Microsponge, controlled release, Febuxostat.

1. INTRODUCTION:

Taking drugs for a long period of time and taking several medicines simultaneously can lead to an increase in noncompliance to the patient. This problem tends to be serious for drugs with short biological half-lives because they must be taken more frequently. The microsponge technology as developed by Won in1987, and the original patents were assigned to Advanced Polymer Systems, Inc. Microsponges are porous microspheres having myriad of inter connected voids of particle size ranging between 5 and 300 µm. They are used as a carrier system since they have the capacity to entrap a wide range of actives in their non-collapsible structures with porous surface, through which active ingredients are released in a controlled manner.[1] microsponge are design to deliver a pharmaceutical active ingredient efficiently at minimum dose and also to enhance stability, flexibility in formulation, reduce side effect and modify release profile.[2] Drug release also is affected by particle size. Smaller particles have a larger surface area-to-volume ratio; therefore, most of the drug associated with small particles would be at or near the particle surface, leading to faster drug release. In contrast, larger particles have large cores, which allow more drugs to be encapsulated per particle and give slower release. Thus, control of particle size provides a means of tuning drug release rates.[3] By encapsulating a drug in a polymer matrix, which limits access of the biological fluid into the drug until the time of degradation, micro-particles maintained the blood level of drug within a therapeutic window for a prolong time period. To maintain the constant plasma drug concentration, the drug should be administered in a constant manner. Hence a controlled release dosage form is required to avoid the repeated drug administration and to improve the patient compliance.[4]

The chemical name of Febuxostat (FEB; Figure 1) is [2-(3-cyano-4-isobutoxy phenyl)-4-methyl-1,3-thiazole-5-carboxylic acid].Febuxostat is a thiazole derivative and inhibitor of Xanthine Oxidase that is used for the treatment of hyperuricemia in patients with chronic GOUT. Febuxostat is an orally available, non-purine inhibitor of xanthine oxidase with uric acid lowering activity. Upon oral administration, Febuxostat selectively and noncompetitively inhibits the activity of xanthine oxidase, an enzyme that converts oxypurines, including hypoxanthine and xanthine, into uric acid. By inhibiting xanthine oxidase, uric acid production is reduced and serum uric acid levels are lowered. [5] FEB received marketing approval by the European Medicines Agency on 21 April 2008 and was approved by the US Food and Drug

Administration on 16 February 2009.[6] It has short biological half life, which increases the dosing frequency and the usual oral dosage regimen is 40 to 80 mg.[7]



[Source: IJPSR, 2015; Vol. 6(10): 4236-4242]
Fig.1: Structure of Febuxostat.

2. MATERIALS AND METHOD:

2.1. Materials:

The drug Febuxostat was gifted by Ajanta pharma, Aurangabad. EudragitRS100 was gifted by Evonic Degussa India Pvt. Ltd., Mumbai. Polyvinyl Alcohol and Triethyl citrate were obtained as gift sample from Glenmark Pharmaceuticals, Sinnar, Nashik. All other chemicals and solvents were of analytical grade.

2.2. Method for Preparation of Febuxostat Loaded Microsponges: [8,9,10]

The microsponges of Febuxostat were prepared by using quasi emulsion solvent diffusion technique. The internal phase was prepared by dissolving Drug and polymer in ethanol in the ratio 1:1, 3:1, 5:1, 7:1, 9:1, 11:1, 13:1 followed by addition of triethyl citrate. The internal phase was then poured into aqueous solution of polyvinyl alcohol, the external phase, and kept for continuous stirring and heating. After 3 hrs of continuous stirring and heating, the microsponges were formed due to evaporation of alcohol. Then the microsponges were filtered and dried at room temperature for 24hrs. The composition of microsponges formulations are given in table 1.

Table 1: Composition of Various Microsponge Formulations.

Ingredients	Ratios (Drug: Polymer)						
	1:1	**3:1**	**5:1**	**7:1**	**9:1**	**11:1**	**13:1**
Febuxostat(mg)	50	150	250	350	450	550	650
Eudragit RS 100 (mg)	50	50	50	50	50	50	50
PVA (mg)	3	3	3	3	3	3	3
Ethanol (ml)	3	3	3	3	3	3	3
TEC (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
DW (ml)	60	60	60	60	60	60	60

3. EVALUATION OF FEBUXOSTAT LOADED MICROSPONGES:

3.1. *Particle Size Determination*:[11]

Average particle diameters of drug loaded microsponges were determined by Digital MOTIC Microscope. The small amount of microsponges was taken on glass slide and slide was placed on stage of microscope. Then the coarse and fine adjustment was done to obtain the clear image. The reading of particle size was displayed on the display of computer. Same procedure was repeated for all batches.

3.2. *Surface Morphology*:[11]

Scanning electron microscopy of optimized microsponge formulation was carried to study the surface morphology. Dried Microsponges were coated under gold palladium alloy for 45 sec under an argon atmosphere before observation. SEM photograph was recorded at the different magnification. SEM study indicated that the microsponges produced by Quasi-emulsion solvent diffusion method are spherical and porous surface.

3.3. *Differential Scanning Calorimetry*:[12]

Differential Scanning Calorimetry was performed on a Lab. METTLER, STAR SW 10.00. The structural, crystal and physical state characterization of Febuxostat, the DSC study was performed for pure drug, and formulation. Accurately weighed sample of drug and formulation was placed in a sealed aluminium pans before heating under nitrogen flow (20 ml/min) at a scanning rate of 10℃ per min from 25℃ to 300℃. An empty aluminium pan was used as a reference.

3.4. *Loading Efficiency and Production Yield*:[13,14]

3.4.1. *Loading Efficiency*:

Febuxostat loaded microsponges equivalent to 10 mg of the drug was taken in a 100 ml standard flask. 25 ml ethanol and 25ml of 6.8 pH phosphate buffer were added and shaken for about half an hour and the volume was made up to 100 ml with 6.8 pH phosphate buffer. 2 ml of the solution was taken and diluted to 100 ml with 6.8 pH phosphate buffer. The absorbance of the resulting solution was measured by recorded obtained value of maximum wavelength of drug and the content of Febuxostat was calculated. The loading efficiency (%) of the microsponges was calculated by using following formula.

$$\textbf{\textit{Loading efficiency}}\ (\%) = \frac{\textbf{\textit{DCact}}}{\textbf{\textit{DCtheo.}}} \times \mathbf{100}$$

Where, DC act = Actual drug content in microsponges
DC theo. = Theoretical drug content.

3.4.2. *Production Yield*:

The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the weight of the microsponge obtained.

$$\textbf{\textit{Production yield}}\ (\%) = \frac{\textbf{\textit{Wpr}}}{\textbf{\textit{Wth}}} \times \mathbf{100}$$

Where, W pr = Practical mass of Microsponges
W th = Theoretical mass (Polymer + Drug).

3.5. *Porosity*:[15]

Porosity of microsponges was calculated by using following equation.

$$\textbf{\textit{Porosity}}(\%) = \frac{\textbf{\textit{Bulk volume} - \textit{True volume}}}{\textbf{\textit{Bulk volume}}} \times \mathbf{100}$$

To measure the bulk volume, weighed amount of microsponges was poured into 1 ml pipette and the bulk volume was noted to nearest graduated unit and true volume was determined by liquid displacement method.

3.6. *In-vitro Drug Release Study*:[15,16]

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally. Dissolution test was performed in dissolution test apparatus Type II (IP)/ Type I (USP) (ElectrolabTDT08L) for capsules and Type I (IP)/Type II (USP) for marketed preparation. Before the test, microsponges amount which are equivalent to dose of Febuxostat were filled in capsules. For comparison, pure drug filled in capsules and marketed formulations were taken.
The dissolution of microsponges filled in capsules and plain drug filled in capsules were carried out in 900ml of phosphate buffer pH 6.8 at a stirring rate of 50 rpm and temperature of 37±0.5 ℃. Drug release was monitored for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,th hr. Samples (5 ml) were withdrawn at regular time intervals and sink conditions were maintained by replacing an equal amount of fresh dissolution medium. The samples were filtered through whatmann filter paper no.52, and diluted up to 10 ml and analyzed by UV-Visible spectroscopy (Shimadzu 1800, Japan) at obtained value of Febuxostat maximum wavelength of drug using phosphate buffer pH6.8 as blank. Dissolution tests were performed in triplicate.

3.7. *Dissolution Kinetics*:[17]

In order to investigate the mode of release from the microsponges, the release data of optimized formulation was analyzed with the following mathematical models:

3.7.1. *Zero Order Kinetics*:

The equation for zero order kinetic is represented as;

$$\textbf{\textit{K}}_0\textbf{\textit{t}} = \textbf{\textit{W}}_0 - \textbf{\textit{W}}_t$$

Where,
W_0 = initial amount of drug
W_t= amount of drug at time t
K_0=zero order release constant

3.7.2. *First Order Kinetics*:

The equation for zero order kinetic is represented as;

$$\textbf{\textit{log}}\textbf{\textit{Q}}_t = \textbf{\textit{log}}\textbf{\textit{Q}}_o + \frac{\textbf{\textit{K1t}}}{\mathbf{2.303}}$$

Where,
Q_t= amount of drug released in time t
Q_0= initial amount of drug
K_1= first order release constant

3.7.3. *Higuchi Model*:

The simplified Higuchi equation is represented as;

$$Q_t = K_H t^{1/2}$$

Where,
Q_t= amount of drug released in time t
K_H = Higuchi's constant
A linear relationship between amount of drug released (Q) versus square root of time ($t^{1/2}$) is observed if the drug release from the matrix is diffusion controlled.

3.7.4. *Hixson-Crowell Model*:

The simplified equation is represented as;

$$W_0^{1/3} - W_t^{1/3} = K_t$$

Where,
W_0=initial amount of drug
W_t= remaining amount of drug at time t
K= cube root constant.

3.7.5. *Korsmeyer- Peppas Model*:

The Korsmeyer-Peppas model relates drug release exponentially to time. It is described by the following equation;

$$\frac{M_t}{M_\infty} = at^n$$

Where,
Mt/M∞ = fractional release of drug
a = constant incorporating structural and geometric characteristics of the drug dosage form
n= release exponent
The value of n indicates the drug release mechanism. This model is used to analyze the release of drug from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release mechanisms are involved.

3.8. *Stability Studies*:[18]

Stability study of optimized formulation was carried out to point out any chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of optimized Febuxostat loaded microsponge formulation was assessed at 40℃±2℃/ 75% ±5% RH as per ICH Guidelines. The powder of microsponge formulation equivalent to 50 mg of Febuxostat was packed with aluminium strip and stored for six months. Sample was analyzed after six months for drug content and in-vitro dissolution profile.

4. RESULTS AND DISCUSSION:

4.1. *Preformulation study of Febuxostat*:

The organoleptic characters of drug were found same as with the literature study. Solubility analysis of the drug indicated that it practically insoluble in water and soluble in methanol, ethanol.

The melting point of the drug was found to be 206°C, which corresponds to the literature value of 205°C-208°C and proves the identity and purity of the drug was shown in fig.5.
The absorbance maxima of Febuxostat were found to be 315 nm in methanol and calibration curve was prepared, as shown in Fig.

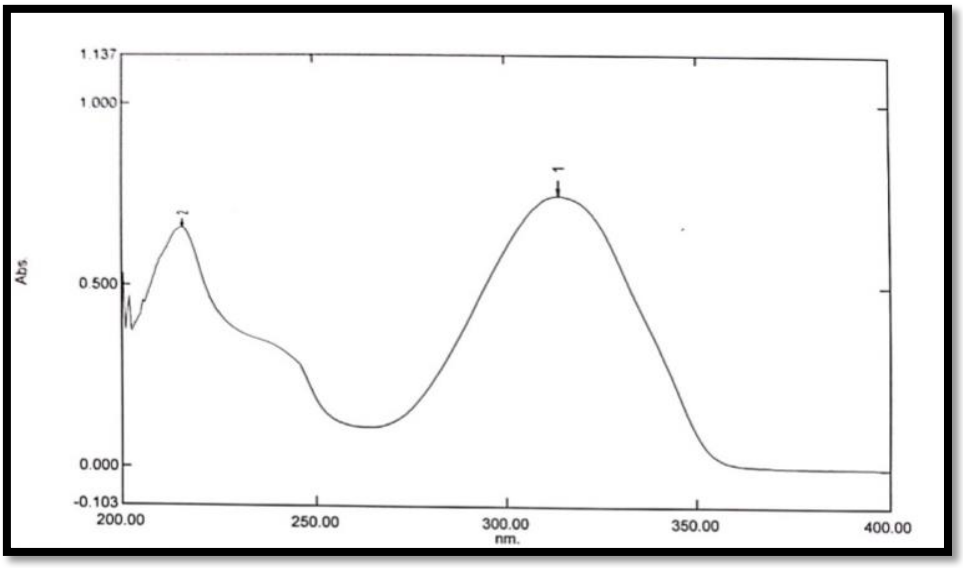


Fig. 1: UV-Visible spectrum of Febuxostat in Methanol

4.2. ***Compatibility Study*:**

4.2.1. ***FTIR Spectroscopy*:**

In the present work, FT-IR spectra of Febuxostat and physical mixture of drug and polymer were examined. In FT-IR spectra of Febuxostat the major peaks at 1731 cm^{-1} which indicates that C=O stretching vibration. 2959 cm^{-1} which indicates that C−H group is present, 2234 cm^{-1} indicates C≡N bond is present, 1675 cm^{-1} indicates C=N bond is present, 1424 cm^{-1} indicates –CH3 group is present. All these peaks were present in physical mixture of drug and polymer. This is an indication of no drug-polymer interaction and hence it can be said that the polymer is compatible with the active pharmaceutical ingredient. The FT-IR spectra of drug and drug with polymer are shown in Fig. 2 and 3.

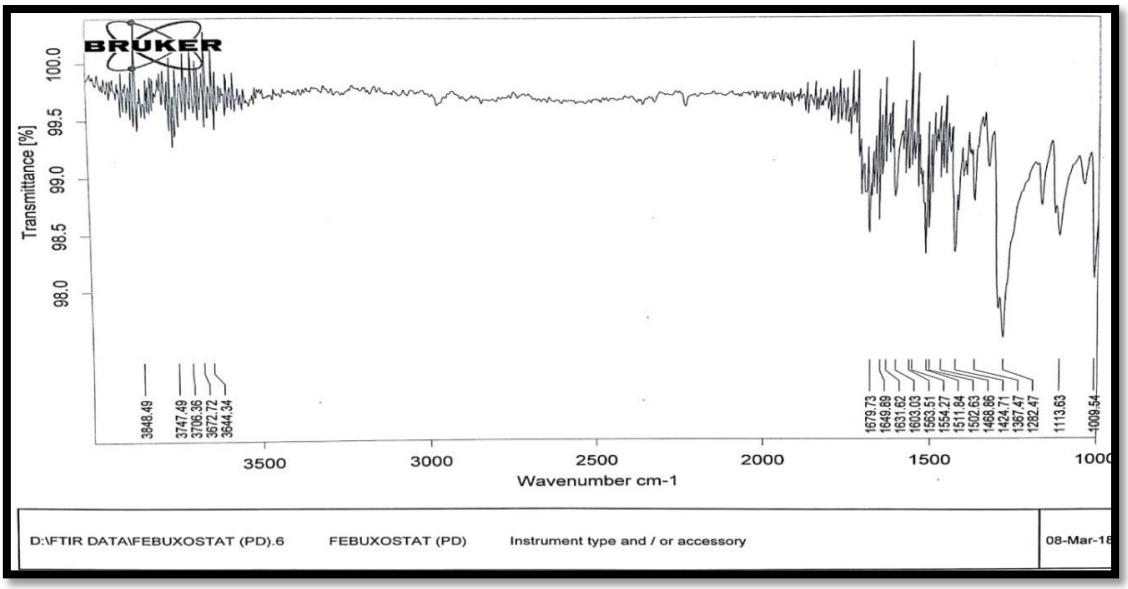


Fig. 2: FTIR Spectrum of Febuxostat.

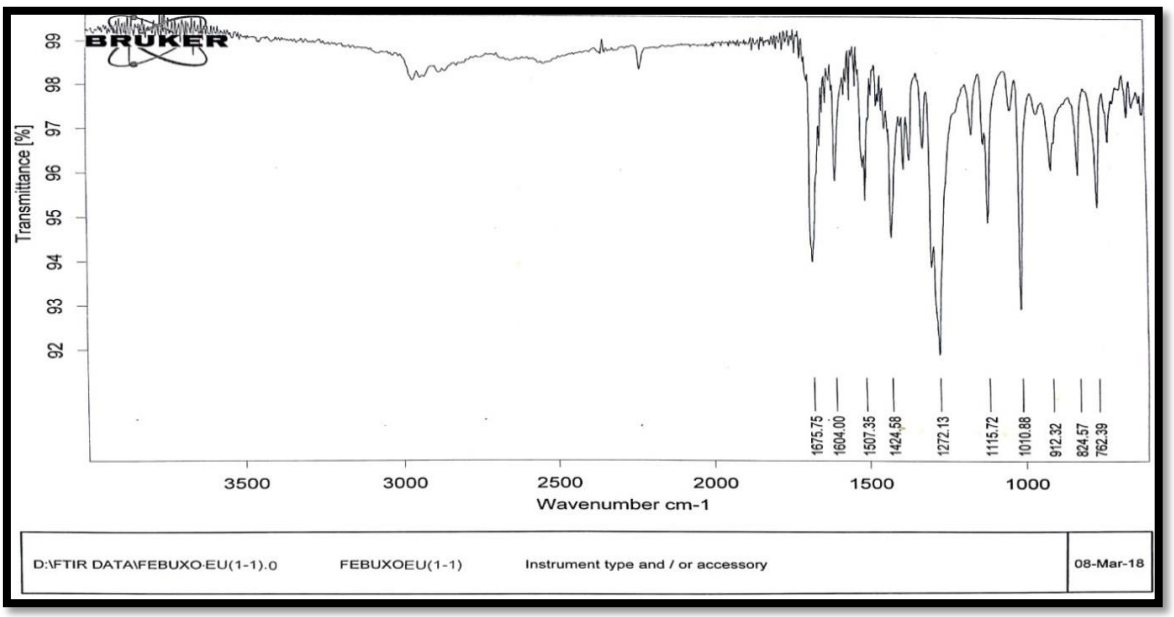


Fig.3: FTIR Spectrum of Febuxostat and Physical Mixture.

5. EVALUATION OF FEBUXOSTAT LOADED MICROSPNGES:

5.1. *percentage yield and Loading efficiency:*

The percentage yields of all formulations were ranging from 32% to 95.16%, Table 2. 11:1 showed highest % yield. Loading efficiency was found ranging from 71.85% to 95.62 % therefore 11:1and 13:1 showed best Loading efficiency, Table 2.

5.2. *Particle Size Determination:*

The microsponges of all ratios were subjected for particle size measurement by using Motic microscope and results of test obtained are shown in table 2. The particle size of the all formulations was ranging from 13.81 µm to 35.06 µm.

5.3. *Porosity*:

Porosity of microsponges was calculated from bulk and true volume. The porosity of microsponges was decreased with increase in concentration of drug in drug: polymer ratio. As the ratio drug: polymer was increased, more amount of drug was available in microsponges which reduces the porosity of microsponges because of non-porous nature of drug. Maximum porosity i.e. 73.73% was found for 1:1 ratio of drug: polymer and minimum porosity i.e. 59.01% was found for 13:1 ratio of drug: polymer. Results obtained from calculation are shown in table 2.

Table 2: Evaluation of Microsponges.

Formulation	Production yield (%)	Loading efficiency (%)±SD	Mean particle size (µm)	Porosity (%) ±SD
1:1	32.00	71.85 ± 1.20	22.41 ± 0.035	73.73 ± 0.078
3:1	53.50	72.55 ± 1.07	13.81 ± 0.020	68.28 ± 0.099
5:1	82.00	79.23 ± 1.02	21.06 ± 0.025	66.22 ± 0.028
7:1	92.50	85.71 ± 1.43	17.72 ± 0.051	64.09 ± 0.014
9:1	93.00	90.91 ± 1.23	18.08 ± 0.035	62.73 ± 0.094
11:1	95.16	95.62 ± 1.00	15.71 ± 0.020	60.21 ± 0.021
13:1	82.28	92.56 ± 1.50	35.06 ± 0.030	59.01 ± 0.055

5.4. *Scanning Electron Microscopy:*

The surface morphology of optimized microsponges formulation was examined by using scanning electron microscope. SEM photograph were recorded at different magnifications. Micrograph at 20.0 Kv and 10.0 µm showed the porous surface of microsponges and it was shown in Fig. 4.

Fig. 4: SEM Photograph of Microsponges Formulation.

5.5. *Differential Scanning Calorimetric Studies*:

DSC thermograph of Febuxostat was shown in figure 5, which shows melting endotherm at 206.79℃ i.e. melting point and crystalline state of drug. DSC thermograph of microsponges formulation was shown in Fig 6. Thermograph

showed melting endotherm at 191.81℃ indicates that drug was embedded in matrix of polymer used.

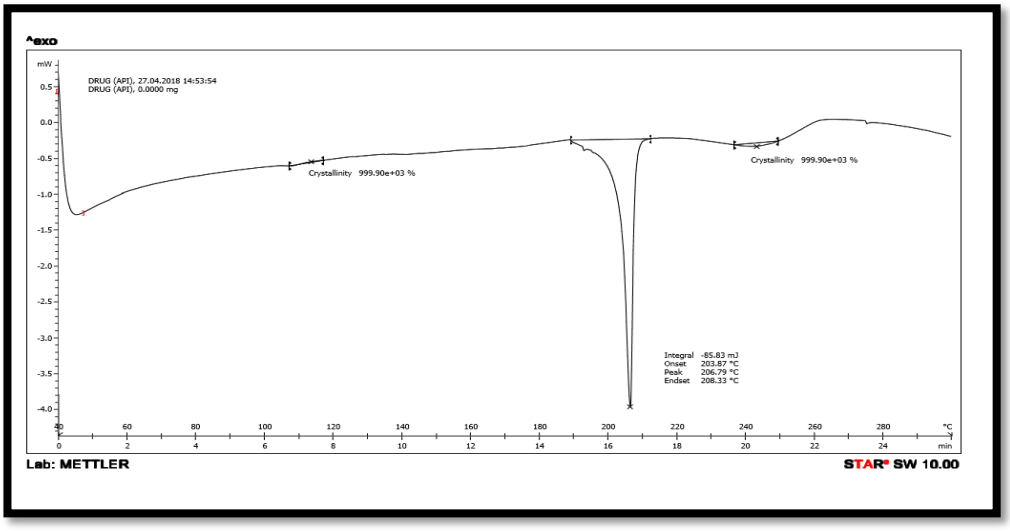


Fig.5: DSC Thermograph of Pure Drug.

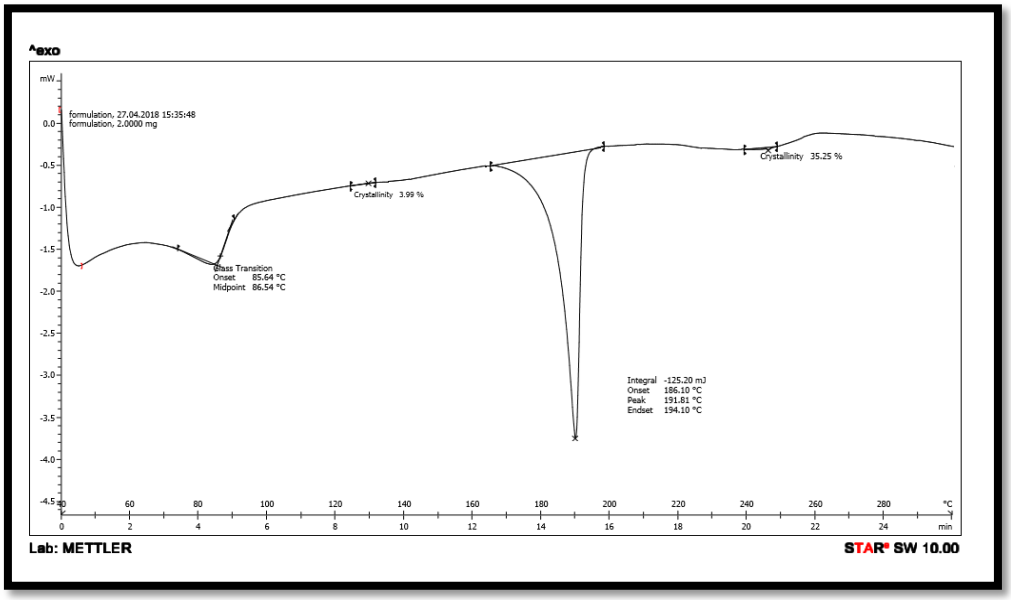


Fig. 6: DSC Thermograph of Optimized Microsponges Formulation.

5.6. *In vitro Drug Release Studies*:

Prepared microsponges were subjected to dissolution test to assess in-vitro release of all formulations. Release study has shown that drug release from the microsponges was in controlled manner as compared to pure drug and it was increased with increase in concentration of drug in drug: polymer ratio up to certain limit i.e. 11:1 ratio of drug: polymer. Controlled release of the drug from microsponges was due to microporous nature of polymer generated in which the drug was entrapped. Maximum drug release i.e. **97.31%** up to 12 hrs was found for formulation containing 11:1 ratio of drug: polymer which may be because of availability of more drug on surface of microsponges. Drug release for 13:1 ratio of drug: polymer was found to be fairly similar to that of 11:1 ratio of drug: polymer. So it can be postulated that there was not considerable change in release pattern after increasing concentration of drug in drug: polymer ratio. Hence 11:1 proportion of drug: polymer should be an ideal and optimized ratio for considering drug release. The pure drug filled in capsules shows **30.38 %** drug release within 1 hrs and shows **98.18%** drug release within

first 6 hrs and marketed formulation shows **81.75%** release which indicates that microsponges has shown better controlled release up to 12 hrs for release of **97.31%** of drug. The comparison of dissolution profile of different microsponges formulation was shown in fig.7 and Comparison of dissolution profile of optimized formulation (11:1) with that of plain drug and marketed preparation was shown in fig. 8.

Table 3: Cumulative Drug Release of Microsponges Formulations.

Cumulative drug release(%)			
Time in (hr)	**Pure Drug**	**11:1 optimized batch**	**Marketed Tablet**
1	30.38 ±0.79	18.26±0.42	13.41±0.28
2	42.73 ±0.80	24.02±0.23	16.70±0.28
3	50.76 ±0.51	32.25 ±0.17	20.19±0.68
4	62.50 ±0.57	41.14±0.18	23.18±0.85
5	87.80 ±0.75	50.04±0.12	30.83±0.41
6	98.18 ±0.17	58.6±0.06	34.05±0.53
7		70.72±0.11	43.11±0.59
8		75.95±0.34	45.95±0.60
9		80.45±0.35	56.29 ±0.55
10		88.75±0.17	61.63±0.23
11		95.10±0.28	72.09±0.34
12		**97.31**±0.68	81.75±0.40

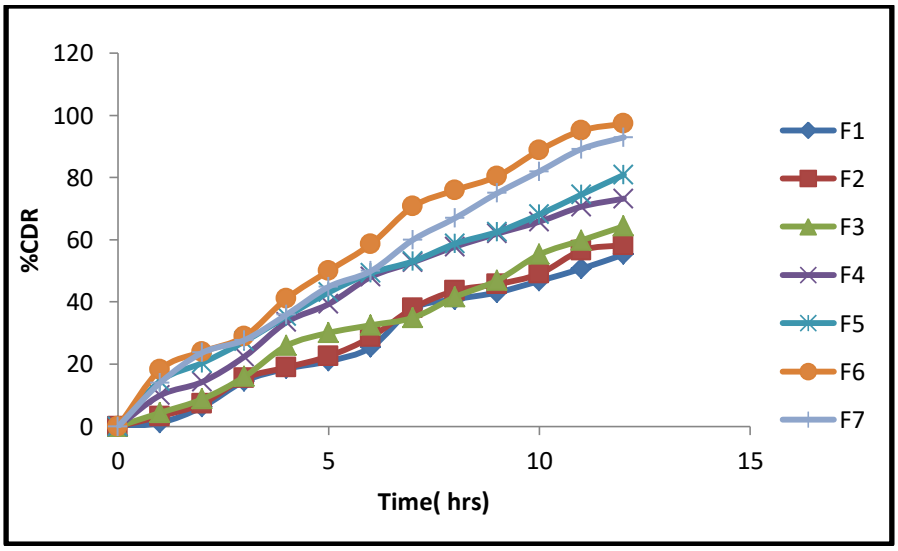


Fig. 7: Comparative In-Vitro Drug Release Profile of Different Ratios of Microsponges.

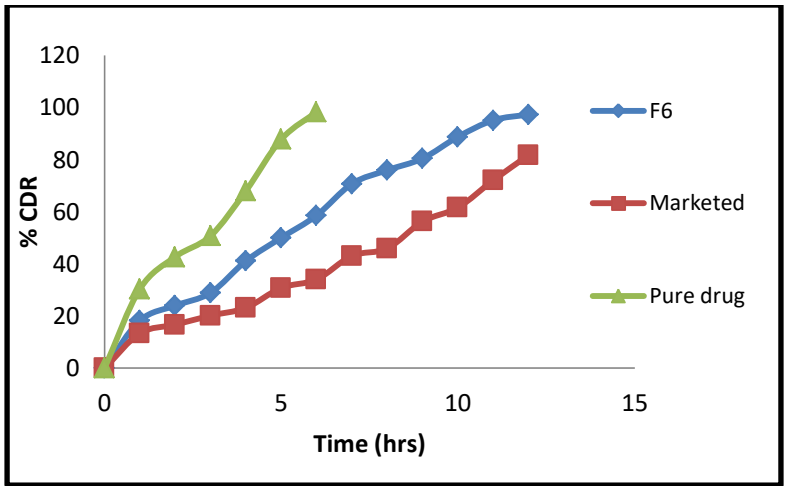


Fig. 8: Comparative In-Vitro Drug Release Profile of Plan Drug, Marketed Tablet and Optimized batch of Microsponges.

5.7. *Release kinetics:*

The present studies of dissolution were analyzed by PCP Disso Version 3 software to study the dissolution kinetics. The results showed that the optimized batch followed korsmeyer-peppas model kinetics. The R^2 value of korsmeyer-peppas model was found close to one as shown in table 4. The Drug Release Kinetics for best fitting optimized batch was calculated and it was shown in table 5.

Table 4: Drug Release Kinetics for Optimized Batch.

Model	R^2
Zero Order Kinetics	0.984
First Order	0.891
Korsemeyer-Peppas Model	0.994
Higuchi Model	0.957

Table 5: Drug Release Kinetic for Optimized Batch.

Sr. no.	Model fitting	R^2 value	N
1	Korsemeyer-Peppas Model	0.994	0.704

The release exponent **n=0.704** indicates that it was following non-fickian release (anomalous), this means that drug release followed controlled release mechanism was shown in fig. 9.

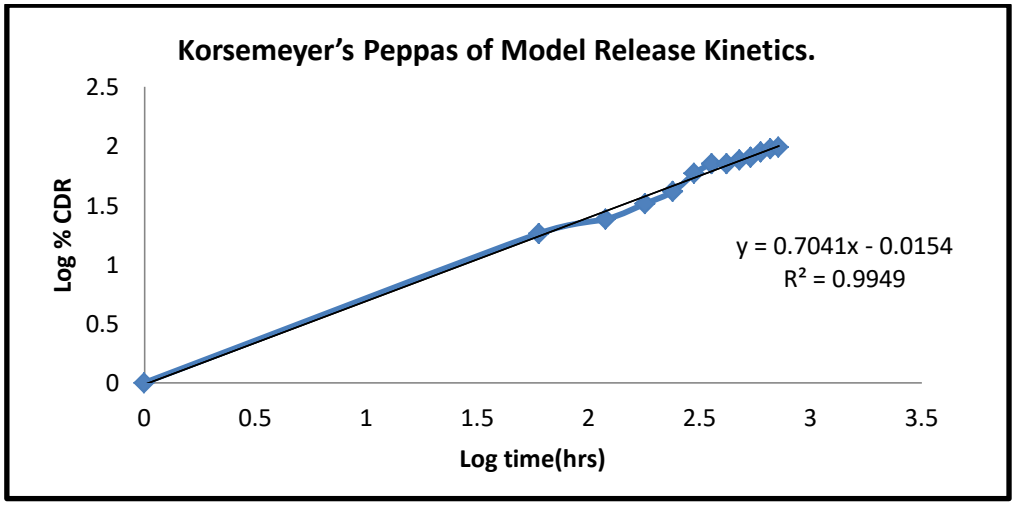


Fig. 9: Model Graph for Evaluation of Korsemeyer's Peppas of Model Release Kinetics.

5.8. Stability Study:

Optimized formulation was subjected to stability studies as per ICH guidelines. Parameters such as drug content and in-vitro drug release were measured before and after six months of stability. Results of stability studies are shown in table 6. Physical appearance of optimized formulation was unaffected or did not show any significant change.

Table 6: Stability Study of Optimized Formulation.

Sr. No.	Stability Parameters	Before Stability Testing	After Stability Testing
			Six Months
1	Drug Content (%) ± SD	95. 62 ± 1.00	94. 41 ±0. 54
2	In-vitro drug release study (%) ± SD	97. 31 ± 0.68	96. 44 ±0. 64

CONCLUSION:

From results obtained after various evaluations it can be considered that microsponges can be formulated using quasi emulsion solvent diffusion technique. Thus, this study presents a new approach for the preparation of modified microsponges with controlled release behavior over a prolonged duration of time which may reduce dose related side effects. The prepared microsponges exhibited characteristics of an ideal delivery system.

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