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FORMULATION AND EVALUATION OF MICROSPONGES OF DICLOFENAC SODIUM

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ABSTRACT

Diclofenac sodium containing micro sponge as active constituent (API) in different formulations by changing the proportions of drug (diclofenac sodium), polymer (ethyl cellulose), emulsifier (Poly vinyl alcohol) were obtained successfully using quasi-emulsion solvent diffusion method.The micro sponges formulations were prepared by quasi emulsion solvent diffusion method employing ethyl cellulose as a polymer. The compatibility of the drug with formulation components was established by Fourier Transform Infra-Red (FTIR) spectroscopy. The surface morphology, particle size, production yield, and drug entrapment efficiency of micro sponges were examined. Shape and surface morphology of the micro sponges were examined using scanning electron microscopy. Particle size of prepared micro sponges was observed in the range of 28.7 ± 1.02 to 23.9 ± 1.19 µm. Scanning electron microscopy revealed the porous, spherical nature of the micro sponges. SEM photographs revealed the spherical nature of the micro sponges in all variations; however, at higher ratios, drug crystals were observed on the micro sponge surface. Increase in the drug/polymer ratio (1:1 to 1:10) increased their yield (10.85 ± 1.60 to 41.03 ± 1.26), average particle size of all formulations ranges from 28.7 µm to 45.9 µm which is in increasing order due to the increase in the concentration of polymer but after certain concentration it was observed that as the ratio of drug to polymer was increased, the particle size decreased, the drug content of different formulations was found in the range 19.07 ± 2.21 to 33.09 ±2.27, the cumulative release of the formulations are in the range of 89.83% to 13.25%.

KEYWORDS: Ethyl Cellulose, Micro sponge Delivery System (MDS). Scanning Electron Microscopy (SEM), UV Spectroscopy.

INTRODUCTION

Microsponges are tiny, sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. Micro sponge delivery systems (MDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. The micro sponge drug delivery technology is widely applicable to the dermatological drug delivery products. But MDS also expands its application in oral drug delivery, bone and tissue engineering, in detecting the diseases and in RNAi silencing.[1] The proposed work involves formulation and evaluation of Diclofenac sodium micro sponge formulation by using Ethyl Cellulose as polymer by quasi emulsion process. Hence, in the present work an attempt was to develop controlled release micro sponges using synthetic polymer to minimize frequent dosing, prolong the pharmacological effect and thus improve patient compliance.

MATERIALS AND METHODS

Diclofenac sodium is a gift sample from Sahyadri Scientific Research Islampur. Ethyl Cellulose, PVA and Carbopol 940 were purchased from Sahyadri Scientific Research Islampur.

Method of Preparation of Micro sponge

Micro sponges of Diclofenac Sodium and Ethyl Cellulose was prepared by quasi-emulsion solvent diffusion method according to the formula given in table no 1, the process involved formation of quasi-emulsion of two different phases i.e. internal phase and external phase similar to emulsions. Table no 1 gives the detailed information about the prepared formulations.

Table 1: Table revealing the master formula for microsponge formulation.

Sr. No.	Ingredient (mg/ml/gm)	F1	F2	F3	F4	F5	F6	F7	F8	F8	F10
1	Diclofenac sodium	1	1	1	1	1	1	1	1	1	1
2	Ethyl cellulose	1	2	3	4	5	6	7	8	9	10
3	Polyvinyl alcohol	500	500	500	500	500	500	500	500	500	500
4	Dichloromethane	10	10	10	10	10	10	10	10	10	10
5	Glycerol	1	1	1	1	1	1	1	1	1	1
6	Water	100	100	100	100	100	100	100	100	100	100
7	Drug: Polymer	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9	1:10

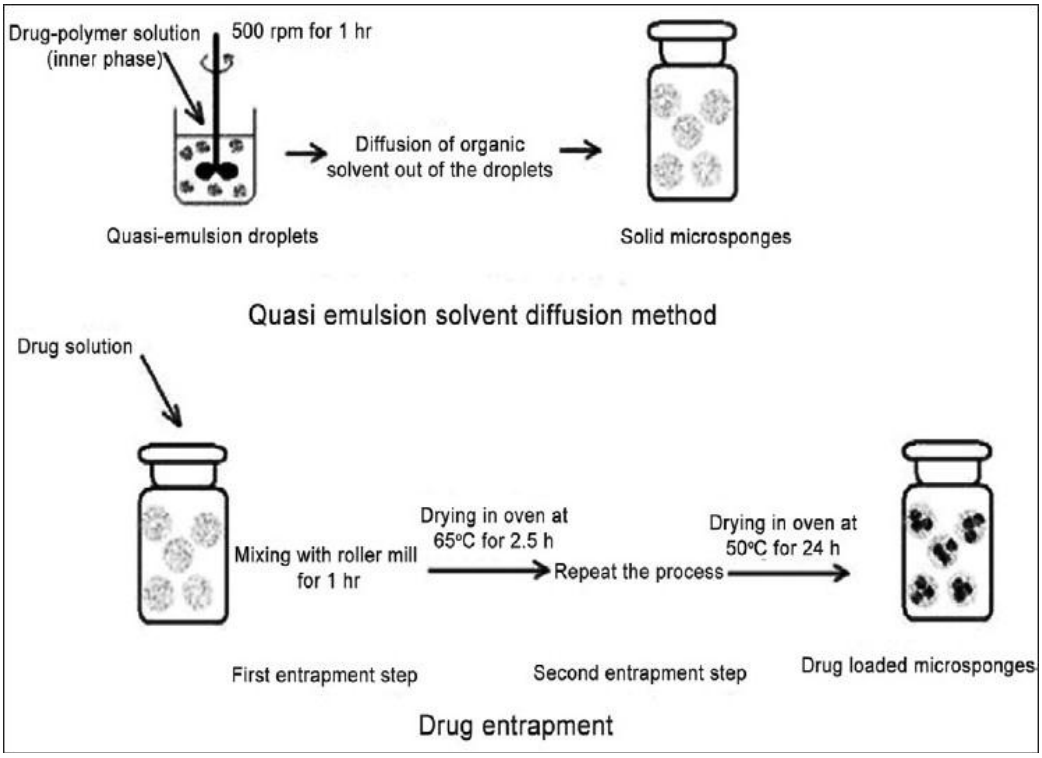

Fig. 1: Image Showing Quasi-emulsion solvent diffusion method set up.

Method of Preparation of Micro Sponge

1) Ethyl cellulose based Diclofenac sodium loaded micro sponge was prepared by quasi-emulsion solvent diffusion method.
2) The internal phase consisted of ethyl cellulose (1 gm) and dissolved in 10 ml dichloromethane.
3) The drug was added to this with gradual stirring (500 rpm). The internal phase was then poured into 0.5 % w/v polyvinyl alcohol (PVA, molecular weight 30,000-70,000) solution in water, the external phase.
4) Glycerol (1-2 ml), which was added at an adequate amount in order to facilitate plasticity. Stirring lead to the formation of discrete emulsion globules called quasiemulsion globules.
5) The stirring was continued upto 6 hrs till the insoluble, rigid micro particles i.e. micro sponges is formed due to removal of dichloromethane from the system.
6) Then it was filtered to separate the micro sponges
7) The micro sponges were then dried in an air heated oven 40°C for 12 hours.[2-4]

Once the formulation was prepared characterization were done by determining percent yield, drug content, particle size, Fourier Transform Infrared (FTIR), surface morphology by Scanning Electron Microscopy (SEM) and *In-vitro* study.

Evaluation of Drug Loaded Micro sponge

The prepared micro sponges were evaluated for the following parameter:

1) Drug content

100mg of micro sponges were dissolving and made up to the 100 ml in volumetric flask with distilled water, final dilution were made with water to get concentration within Beer's range. The absorbance was made spectrophotometric ally at 276 nm using water as a blank.

2) Entrapment Efficiency[5,6,7,8,9]

The entrapment efficiency (%) was calculated was calculated according to the following equation:

$$\% \text{ Entrapment efficiency} = \frac{\text{Actual drug content in microsponge}}{\text{Theoretical drug content}} \times 100$$

3) Partical size and size Distribution Analysis[9]

The partical size was determined using an optical microscope. The microscope was fitted with a stage micrometer to calibrate the eyepiece micrometer.

Calibration of the Eyepiece Micrometer

One division of stage micrometer = 0.01mm = 10um

C = (SM X 100)/ EM

Where, C = correction factor

SM = reading of stage micrometer which coincides with reading of eye piece micrometer (EM)

The partical diameter of around 200 microsphere were measured at random with optical microscope. The average partical size was determined using the equation

D (mean) = Σ nd/ Σn

Where, n = no. of microsponges observed,

D = mean size range

4) Angle of Repose[10]

In this method weighed 20 gm. of microsponges of diclofenac sodium, passed it through sieve no 40 mesh size .then allowed to flow under gravity though funnel and angle of incline of the formed. That is produced is assayed by measuring the height and having a fixed base i.e. diameter.

Angle of Repose θ = tan –1 h/r

Where

h= height of peak

r = radius of peak base

The standard value and experimental value of angle of repose are shown in Table 4

5) Determination of Density[10]

i. Bulk Density

It is the ratio of total mass of microsponge to the bulk volume of microsponge. It was measured by pouring the weighed microsponge (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by:

Db = m/Vo

Where,

m = mass of the microsponge

Vo = bulk Volume of microsponge.

ii. Tapped Density

It is the ratio of total mass of microsponges to the tapped volume of powder. The volume was measured by tapping the microsponges for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

Dt = m/Vi

Where,

m= Mass of the microsponges

Vi = Tapped Volume of the microsponges.

6) Compressibility index :(Carr's Index)[10]

It is determined by taking tapped density and bulk density. This has been put in the formula given below and determined compressibility index using following Formula.

Tapped density – bulk density / tapped density x 100

7) Hausners ratio:[10]

The Hausners ratio was calculated using formula:

$$\text{Hausners ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Tapped density was determined by placing 5 gm of the microsponges in a graduated cylinder tapping it for 100 times. Poured density was determined by placing 5 gm of microsponges into a graduated cylinder and measuring the volume (Rao and Patil 2005). The standard value and experimental value of Carr's Index and Hausners ratio are shown in Table no7. 4

8. Percentage yield[11]

Percentage yield was determined by following formula:

$$\text{Percentage Yield} = \frac{\text{c (Practical yield)}}{\text{a + b (Theoretical yield)}} \times 100$$

Where,

a- Weight of Tolmetin sodium taken in Microsponges preparation.

b- Weight of Polymer taken in Microsponges preparation.

c- Total weight of microsponges.

9) Determination of FTIR spectrum

About 1mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer USA and the IR spectrum was recorded from 4000 cm-1 to 400cm-1 at resolution of 1 cm-1 in a scan time of 12 minutes. An FTIR spectrum of pure drug (Tolmetin sodium) was obtained. The resultant spectrum was compared for any spectral changes with reference spectra.

10) In-Vitro Drug Release Studies

In-vitro Dissolution Studies[5,6,7,8,9]

Diclofenac sodium (Pure Drug) & Diclofenac sodium loaded Microsponges were subjected to dissolution test using in-vitro dissolution rate USP Apparatus-II. (Paddle method). This test was performed using 900 ml of dissolution medium buffer solution PH 7.4 at 37±2ºC. Accurately weighed samples (plain drug and Diclofenac sodium loaded microsponges) approx. 20mg of drug were added in 900 ml capacity jar of dissolution apparatus which paddle was rotated at 50 rpm. A 5ml aliquot of dissolution medium was withdrawn at appropriate time intervals. An equal volume of fresh dissolution medium was immediately replaced. It was suitably diluted and analyzed spectrophotometrically by measuring absorbance at 276nm. The experiments were performed in triplicate. With the help of standard curve equation concentration were found using absorbance values. For rapidly dissolving product more than 85% of API is expected to dissolve within 30 minutes using USP apparatus I & II in ≤ 900ml of aqueous medium.

RESULTS

1) Drug content

Drug content of Diclofenac sodium Microsponges With polymers were found within the range of 19.07 ± 2.21 to 33.09 ±2.27. With this evaluation parameter of Microsponge it was revealed that the formulation F2 have the Drug content greater i.e. 74.03 mg and after that the drug content is decreasing with increase in content of polymer due to improper carrying of drug by the polymer.

Table 2: Table revealing the results of Drug content studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug content (%) (mean ± S.D) n=3	19.07 ± 2.21	74.03 ± 2.25	27.82 ± 2.12	38.67 ± 2.13	69.85 ± 2.31	63.02 ± 2.16	58.01 ± 2.21	51.06 ± 2.34	3705 ± 2.19	33.09 ± 2.27

2) Entrapment efficiency

Entrapment efficiency of Diclofenac sodium Microsponges With polymers were found within the range of 85±0.06 to 85±0.02. With this evaluation parameter of Microsponge it was revealed that the formulation F2 have the Entrapment efficiency greater i.e. 92.42±0.08.

Table 3: Table revealing the results of Entrapment efficiency studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8F	F9	F10
Entrapment efficiency	85± 0.06	92.42± 0.08	88± 0.06	71.19± 0.09	80± 0.02	75± 0.05	71.19± 0.09	88± 0.04	90± 0.03	85± 0.02

3) Partical size and size distribution analysis

Probably in high drug-polymer ratios less polymer amounts surround the drug and reducing the thickness of polymer wall and microsponges with smaller size were obtained. By performing the particle size analysis, it is concluded that the formulation has the particle size varies with the concentration of polymer drug ratio. Result are described in following table no.:4.

Table 4: Table revealing the results of Partical size and size distribution analysis studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Partical size	28.7 ± 1.02	23.9 ± 1.19	31.8 ± 1.05	33.7 ± 1.54	29.8 ± 1.00	37.2 ± 1.32	31.3 ± 1.25	31.3 ± 1.25	31.9 ± 1.17	29.4 ± 1.23

4) Angle of repose

Angle of repose of Diclofenac sodium Microsponges With polymers were found within the range of $28^{o}.69'$± 1.19 -28 $^{o}.14$ '± 1.02. The result of characterization of tolmetin sodium microsponges given in table No: 5.

Table 5: Table revealing the results of Angle of repose studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Angle of repose	$28^{o}.69'$ ± 1.19	25 $^{o}.34$ ' ± 1.02	26 $^{o}.12$ ' ± 1.54	30 $^{o}.15$ ' ± 1.32	31 $^{o}.56'$ ± 1.25	28 $^{o}.14'$ ± 1.05	26 $^{o}.39'$ ± 1.19	26 $^{o}.38'$ ± 1.25	27 $^{o}.65'$ ± 1.05	28 $^{o}.14'$ ± 1.02

5) Determination of Density

i. Bulk Density

Bulk density of Diclofenac sodium Microsponges With polymers were found within the range of 0.45-0.44gm/cc. The result of characterization of Diclofenac sodium microsponges given in table No: 6.

ii. Tapped Density

Bulk density of Diclofenac sodium Microsponges With polymers were found within the range of 0.43-0.54gm/cc. The result of characterization of Diclofenac sodium microsponges given in table No: 6.

Table 6: Table revealing the results of Bulk Density and Tapped Density studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Bulk Density	0.45	0.40	0.46	0.48	0.42	0.48	0.45	0.60	0.43	0.44
Tapped Density (gm./gm./cc)	0.43	0.42	0.44	0.45	0.46	0.43	0.48	0.51	0.54	0.54

6) Compressibility index

Compressibility of Diclofenac sodium Microsponges With polymers were found within the range of 11.66-22.22%. The result of characterization of Diclofenac sodium microsponges given in table No: **7.**

Table 7: Table revealing the results of Compressibility index studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Compressibility index %	11.66	11.60	15.48	18.65	20.35	14.58	12.27	13.65	21.32	22.22

7) Hausners ratio

Hausners ratio of Diclofenac sodium Microsponges With polymers were found within the range of 0.07-0.16. The result of characterization of Diclofenac sodium microsponges given in table No: 8.

Table 8: Table revealing the results of Hausners ratio studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hausners ratio	0.07	0.06	0.05	0.07	0.08	0.11	0.15	0.08	0.14	0.16

8) Percentage yield

Percentage yield of Diclofenac sodium Microsponges With polymers were found within the range of 80.47-92.36%. The result of characterization of Diclofenac sodium microsponges given in table No: **9.**

Table 9: Table revealing the results of Percentage yield studies.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Percentage yield	80.47	93.24	75.69	89.54	79.01	75.36	80.47	83.24	87.45	92.36

9) FTIR Spectroscopy

FTIR Spectra of Microsponges of Diclofenac sodium in comparison with pure drug was done to determine the interaction between drug and polymer. Result of FTIR graph is shown in following figure.

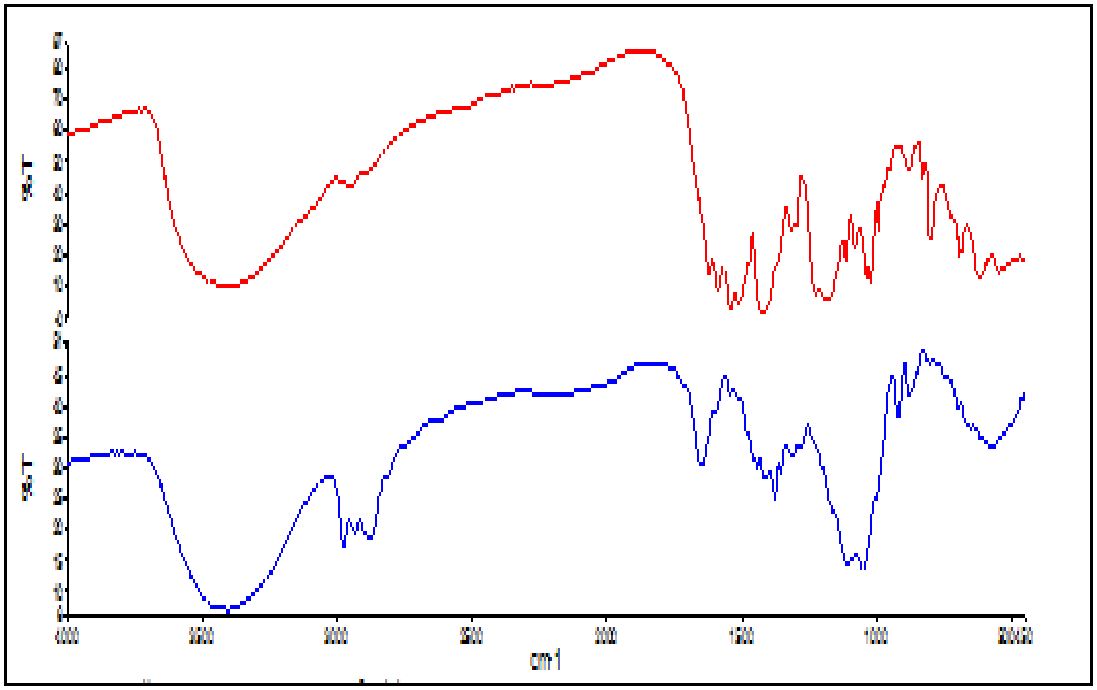

Figure 2: Comparative FTIR Spectra of Diclofenac sodium & microsponges.

10) *In Vitro* Drug release through microsponge

Table 10: Table Revealing the Results of % Drug Release Studies.

Sr. No.	Percent Drug Release										
	Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	0	0	0	0	0	0	0	0	0	0	0
2	5	3.69	3.31	3.66	3.74	3.71	3.63	3.26	3.61	3.69	3.45
3	10	5.87	5.48	5.85	5.74	5.99	5.47	5.29	5.49	5.94	5.6
4	15	8.03	8.31	8.11	7.98	10.48	8.49	7.89	8.45	8.16	9.41
5	20	12.33	12.56	11.63	11.93	13.51	13.46	12.26	13.33	13.36	13.45
6	30	15.01	16.84	15.02	15.49	15.98	16.21	16.28	16.98	17.01	16.54
7	45	18.62	20.65	18.04	18.57	18.62	18.68	18.21	18.56	18.09	18.45

8	60	20.64	25.69	20.56	20.56	20.79	20.86	20.83	20.21	20.61	19.64
9	120	23.79	35.47	24.84	23.82	29.37	22.01	24.67	21.09	22.87	21.47
10	180	29.36	49.35	30.14	28.84	41.78	30.11	24.76	29.78	26.18	27.25
11	240	36.07	60.25	41.33	35.81	50.51	41.47	31.48	38.96	35.37	36.87
12	300	41.55	75.01	52.77	40.99	62.7	52.57	38.75	48.45	42.07	43.57
13	360	49.74	80.24	60.56	48.48	75.38	61.45	44.79	62.7	55.93	54.17
14	420	55.4	85.65	72.66	54.96	84.92	74.84	49.28	67.78	70.18	71.58
15	480	61.65	90.27	78.62	60.13	90.27	80.36	53.43	71.34	76.39	75.14
16	540	69.59	94.67	83.85	67.55	93.04	83.19	60.52	74.87	80.37	80.34
17	600	75.71	96.35	87.94	73.15	95.69	89.49	67.16	77.83	85.97	84.68
18	660	89.83	97.65	89.13	88.31	96.71	92.49	80.62	83.50	89.17	90.47
19	720	95.47	98.99	90.56	94.52	96.35	96.54	95.68	97.84	89.57	91.01

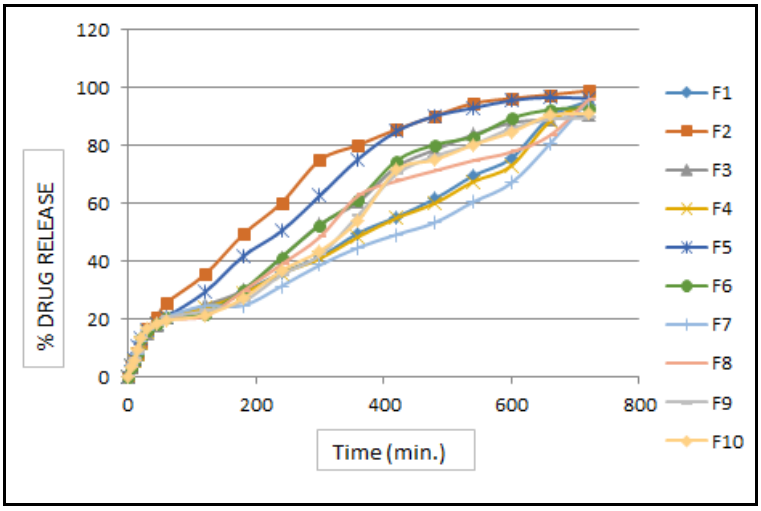

Figure 3: % Drug Release of Diclofenac Sodium Microsponges.

CONCLUSION

The micro sponges were prepared by quasi emulsion method and were evaluated for its different parameters which revealed many interesting results for efficient preparation of the micro sponges. The formulation F2 has better results than other 9 formulations. F2 have its particle size 23.9 ± 1.19, percentage yield 93.24 %, Drug content 74.03 ± 2.25, and Entrapment efficiency 92.42±0.08, Cumulative Release 98.99 % in 12 hour, all these parameters are in optimized range for preparing a controlled release dosage form so showing itself as an optimized formulation in this project work. FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these micro sponges. However, at higher ratios, drug crystals were observed on the micro sponge surface. With the revealed results by different evaluation parameters, it is concluded that micro sponges drug delivery system has become highly competitive and rapidly evolving technology and more and more research are carrying out to optimize cost-effectiveness and efficacy of the therapy. It is a

unique technology for the controlled release of drug and consists of micro porous beads loaded with active agent and also use for oral as well as biopharmaceutical drug delivery. Micro sponge delivery systems can precisely control the release rates or target drugs to a specific body site have a vast impact on the health care system. A micro sponge delivery system can release its active ingredient on a timer mode and also in response to other stimuli. Therefore, micro sponge has got a lot of potential and is a very emerging field which is needed to be explored. Micro sponges constitute a significant part by virtue of their small size and efficient carrier characteristics.

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