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Topical Anti-Inflammatory Gels of Naproxen Entrapped in Eudragit Based Microsponge Delivery System

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Abstract

Naproxen is a medium potency, synthetic, non-steroidal anti-inflammatory drug, indicated for the relief of inflammation. Non-steroidal anti-inflammatory drug`s oral administration contraindicated in patients with peptic ulcer disease, gastro esophageal reflux (GERD), irritable bowel syndrome, or other gastrointestinal disorders. Controlled release of the drug to the skin could reduce the above mentioned side effects related to oral administered drug formulation while reducing percutaneous absorption. Therefore, the aim of present study was to produce naproxen entrapped micro porous micro particles (micro sponges) to control the release of the drug to the skin. Naproxen micro sponge was prepared using quasi emulsion solvent diffusion method. In order to optimize the micro sponge formulation, factors affecting the physical properties of micro sponges were determined. Compatibility of the drug with excipients was studied by FT-IR. Production yield, loading efficiency and surface morphology of micro sponges were performed. It was shown that the drug: polymer ratio and stirring rate influenced the particle size and drug release behaviour of micro sponges. The results showed that, generally an increase in the ratio of the drug: polymer resulted control release rate of naproxen from micro sponges.

Keywords: Micro sponges; Gel; Naproxen; Anti-inflammatory

Introduction

A micro sponge delivery system (MDS) is highly cross linked, patented, porous, polymeric microspheres which consists of micro porous beads normally 20-200 microns in diameter that acquire the flexibility to entrap a wide variety of active ingredients such as emollients, fragrances, sunscreens, essential oils, anti-infective, anti-fungal and anti-inflammatory agents etc., that are mostly used for prolonged topical administration [1,2]. Polymers are important in the field of drug delivery for their use as binders, viscosity, flow controlling, film coatings, to modify drug release characteristics. Controlled drug delivery systems include the maintenance of drug levels, administrations, increased patient compliance. The development of an ER micro sponge gel formulation of a drug is to enhance its therapeutic benefits and minimize its side effects, while improving the management of the disease condition [3,4]. Thus, control release microsponges delivery systems to maximize the period of time that an active ingredient on the skin surface or within the epidermis while minimizing its transdermal penetration into the body. Non-steroidal anti-inflammatory drugs are used to treat pain, inflammation and fever with relatively high adverse reactions in gastrointestinal track [5,6]. Naproxen is a phenylpropionic acid derivative having analgesic, anti-inflammatory and antipyretic activity. Such activity is thought to be mediated via inhibition of the enzyme complex prostaglandin synthetase with consequent reduction in the synthesis of prostaglandins from arachidonic acid. Naproxen also inhibits platelet aggregation by inhibition of platelet thromboxane A2. The onset of action of naproxen may be 2 or more hours after oral administration with therapeutic effects persisting for up to 7-8 hours. Topical delivery is used for local and systemic treatment. The delivery of drugs onto the skin is recognized as an effective means of therapy for local dermatologic diseases. It can penetrate deeper into skin and hence give better absorption [7]. In order to increase therapeutic efficacy after topical application of drugs, it is necessary to employ percutaneous absorption enhancer and/or appropriate vehicles. An attempt has been made, to enhance the transdermal permeation of naproxen gel. The present study aims to evaluate the efficacy of naproxen gel formulations for transdermal delivery of naproxen via in vitro and in vivo study.

Materials and Methods

Materials

Naproxen powder was supplied by Wockhardt Pharmaceuticals Ltd., Aurangabad, Eudragit polymers (RS-100) powder were obtained from Evonik Industries, Mumbai, polyvinyl alcohol (PVA) and carbopol from Loba chemie, India. All other materials used in this study were of analytical grade.

Methods

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 8 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 [8]. The composition ratio and stirring rate for various microsponge formulations is given in Table 1.

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Characterization and evaluation of microsponges formulation

Determination of the production yield: The production yield of the microsponge was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained Table 1 [9].

$$\text{Production yield} = \frac{\text{Production mass of microsponge}}{\text{Theoretical mass (Drug+Polymer)}} \times 100$$

Determination of loading efficiency (Percentage entrapment efficiency analysis): The weighed amount of drug loaded microsponges equivalent to (100 mg) was kept in 100 ml 6.8 phosphate buffer for 12 hrs with continuous stirring. The samples were filtered using 0.45 µm membrane filter and the samples were analyzed at 230.0 nm against blank using UV spectrophotometer (Shimadzu, Japan). The drug content and encapsulation efficiency were calculated using the following formula Table 1 [9].

$$\text{Encapsulation Efficiency} = \frac{\text{Mact}}{\text{Mthe}} \times 100$$

Formulas	Ratio Naproxen: Eudragit (100 mg)	Practical Yield ˚(mg)	Production Yield ˚(%)	Drug content (%)	Loading capacity (%)	Stirring (RPM)
F1	1:1	115 ± 1.17	57.5 ± 0.588	17.49	58.33	300
F2	1:2	160 ± 1.17	53.3 ± 0.38	15.41	77.03	
F3	1:3	220 ± 1.26	55.0 ± 0.31	11.42	76.13	
F4	1:4	320 ± 3.66	64.0 ± 0.73	7.4	64.15	
F5	1:5	432 ± 3.75	72.1 ± 0.62	7.8	78.11	
F6	1:1	118 ± 2.10	59.0 ± 0.48	17.55	58.33	400
F7	1:2	190 ± 0.25	63.3 ± 0.06	12.3	61.59	
F8	1:3	210 ± 1.55	52.5 ± 0.39	10.61	70.74	
F9	1:4	325 ± 0.41	65.0 ± 0.22	8.3	69.63	
F10	1:5	438 ± 3.66	73.0 ± 0.31	18.15	81.56	
F11	1:1	113 ± 3.75	56.5 ± 0.73	18.01	61.04	500
F12	1:2	186 ± 2.10	62.0 ± 0.62	13.66	68.34	
F13	1:3	250 ± 0.25	62.5 ± 0.48	10.20	68.80	
F14	1:4	310 ± 1.55	64.0 ± 0.06	8.3	79.13	
F15	1:5	432 ± 0.41	72.0 ± 0.39	7.4	74.35	

Table 1: The composition of micro sponges formulas.

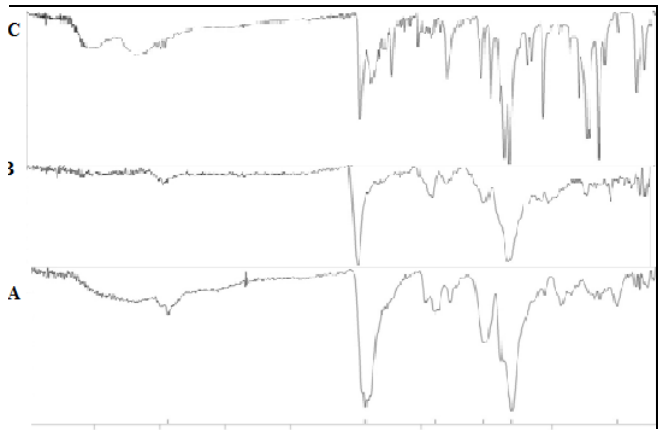

Figure 1: FT-IR Spectra of: A) Microsponge formulation F10. B) Eudragit RS-100. C) Naproxen.

Fourier transform infrared (FTIR) spectroscopy: FTIR spectra of pure naproxen, physical mixture of naproxen/eudragit RS-100 (1:2.5:0.2) and optimized microsponge formulation were recorded with a Bruker FT-IR instrument (Germany) from 4000-400/cm using KBr pellets. The pellets were made by applying a pressure of 100 kg/cm^2 to a mixture of eudragit RS-100 and KBr (1:20) for 10 min in a hydraulic press (KP, Kimaya Engineers, India) (Figure 1).

Scanning electron microscopy (SEM)

Surface topography of the selected optimized formulation was characterized using scanning electron microscopy (SEM). Freshly prepared microsponge samples were mounted on the aluminium stub and coated with gold-palladium layer by auto fine coater (Joel, JFC, Tokyo, Japan) and analyzed with a scanning electron microscope (Joel, JSM-6360, Tokyo, Japan) operated at a 10 kV acceleration (Figure 2).

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed by differential scanning calorimeter 60 Schimadzu to obtain suitable thermo grams. The accurately weighed sample was placed in an aluminium pan and an empty aluminium pan was used as reference. The experiment was performed under nitrogen flow, at a scanning rate 300°C/min in range of 50-350°C (Figure 3).

Particle size analysis

Particle size analysis of prepared microsponges was carried by using Malvern particle size analyzer. Microsponges were dispersed in double distilled water before running sample in the instrument, to ensure that the light scattering signal, as indicated by particles count per second, was within instrument's sensitivity range (Figure 4).

Drug release studies

The in vitro drug release of microsponges gel were prepared and formulated and was studied through cellophane membrane using modified apparatus. The dissolution medium was freshly prepared phosphate buffer pH 6.8. Cellophane membrane was previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder. 100 mg equivalent gel formulation of naproxen microsponge was kept in donor compartment. The cylinder was attached to stand and suspended in 32 ml of dissolution

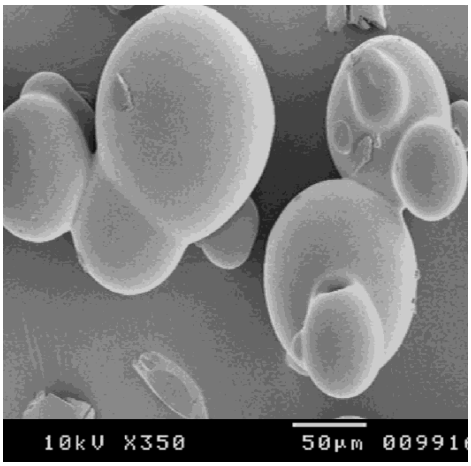

Figure 2: SEM of naproxen microsponges.

medium maintained at 37 ± 0.5°C, the membrane just touching the receptor medium surface. The dissolution medium was stirred at 100 rpm speed using magnetic bead. Aliquot, each of 2 ml were withdrawn periodically at determined time interval of 30, 60,120, 180, 240, 300, 420, min and replaced by equal volume of the receptor medium. The aliquot were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 230 nm using phosphate buffer as blank (Table 2) [10].

Rheological characterization

Rheological measurements of the microsponge loaded gel and blank gel were performed using a Brookfield's RVDV-II+ model viscometer (Brookfield Engineering Laboratories; Middleboro, MA, USA). Data analysis was done with stress rheological basic software, version 5.0. A cone and plate geometry was used with 25 mm diameter and cone of 1.0o [11]. Fresh sample was used for test and all measurements were carried out in triplicate at 25°C (Table 3).

Formulation of naproxen micro sponge gel (G1-G5)

A clear dispersion of carbopol (100, 70, 80, 50 and 60 mg) and HPMC (50, 30, 40, 25 and 40 mg respectively for G1, G2, G3, G4 and G5) in water using moderate agitations than glycerin was added . Naproxen loaded microsponges 600 mg were dispersed in propylene glycol and ethanol 5 ml each. Triethanolamine q.s.was used to neutralize and volume was made with water 10 ml. Gels prepared were degassed by ultrasonication.

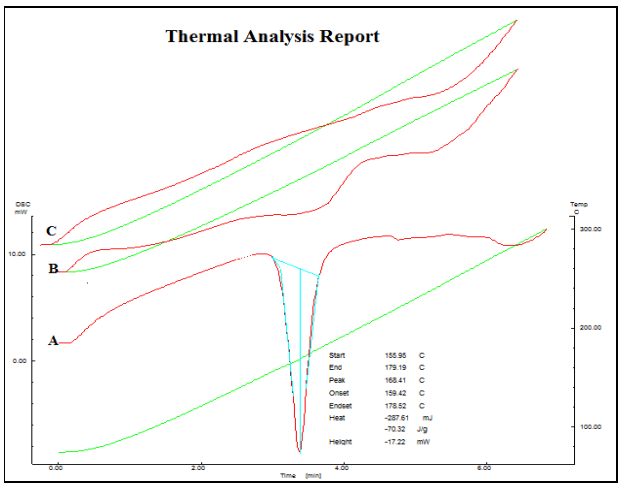

Figure 3: FDSC of A) Naproxen. B) Eudragit RS-100. C) Microsponge formulation F10.

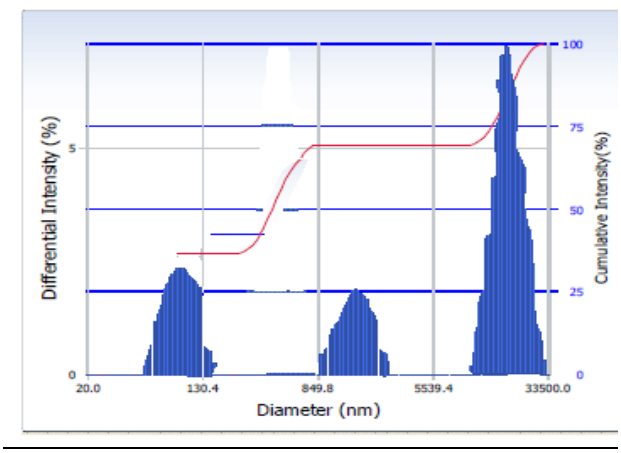

Figure 4: Particle size distribution of drug-loaded Eudragit RS-100 microsponges F10.

Skin irritation test

Approval to carry out these studies was obtained from the Institutional Animal Ethics Committee (IAEC) (1211/PO/ac/08/CPCSEA).

Skin irritation test of optimized naproxen loaded microsponge gel (G3) was compared with the marketed and placebo gel. The present study was employed in the three groups of rats (n=6) to evaluate skin irritation. They were kept carefully following an acclimation period of 7 days to ensure their suitability for the study. Test animals were kept within a limited-access rodent facility with environmental conditions set to a temperature of 25 ± 2°C, a humidity of 60-90% RH, and a 12-h light/12-h dark cycle. Animals were provided ad labium access to a commercial rat diet and drinking water was supplied to each cage. The area on the back of each rat was shaved prior to the experiment. The first group of the rat was applied with microsponge gel and the second group was applied with commercial naproxen gel. The remaining group of rats was considered as a control group. The 0.5 g of each test product was placed on each area (25 × 25 mm) for 30 minutes. Finally treated skin area of rats was washed off by tap water. Scoring of the erythema was performed at 24 and 72 hours and both the treated and controlled sites were covered and wrapped by cotton bandage. Reactions on skin were measured after 24 hr and 72 hr in form of erythema. The mean erythemal scores were recorded (ranging from 0 to 4) according to Draize scale [12]. The responses of all the formulations applied on rat skin surface were evaluated and primary irritation index (PII) was calculated and matched with response category as shown in Table 4.The score of primary irritation was calculated for each rat. Scores for erythema at 24 and 72 hours were summed and divided by the number of the observations for the treated sites [10].

Stability study

Stability study was conducted for prepared micro sponge formulation gel G3 as per ICH guidelines, kept at 40 ± 2°C with RH of 45% for a period of 90 days. Formulation was evaluated at periodical interval of 1 month for pH, drug content and drug release (Table 5).

Results and Discussion

Formation of micro sponges

Different Naproxen: Eudragit (w/w) ratios (1:1, 1:2, 1:3, 1:4 and 1:5) were tested for the preparation of micro sponges setting the speed at 300, 400 and 500 rpm (Table 1). Scanning electron microscopy revealed that all the micro sponges were porous, spherical but the porous nature was more prominent in F10 and no drug crystals were visible on the micro sponge surface at batch. Further increase in speed i.e. 500 rpm agglomeration of the micro sponge were observed .The

Formulation	Kinetic model	R^2 value
F10	Peppas equation	0.99 ± 0.06
F10	Matrix equation	0.98 ± 0.14
F10	1st order equation	0.96 ± 0.09
F10	Hix Crow	0.95 ± 0.08

Table 2: *In vitro* release kinetics of optimized formulations.

Time (s) t	Torque	Speed(1/min)	Shear Stress	Share Rate	Viscosity	Temperature(° c)
6	6.34	1.67	57.40	10.03	5.72	25.0
12	8.19	3.34	74.19	20.02	3.71	25.0
18	9.59	5.01	86.82	30.03	2.89	25.0
24	10.66	6.67	96.48	40.01	2.41	25.0
30	12.56	8.34	105.82	50.02	2.12	25.0
36	13.43	10.00	113.71	60.02	1.89	25.0
42	14.16	11.67	121.62	70.01	1.74	25.0
48	14.83	13.34	128.22	80.02	1.60	25.0
54	15.50	15.00	134.25	90.02	1.49	25.0
60	15.50	16.67	140.33	100.03	1.40	25.0
66	15.94	16.67	140.31	100.01	1.40	25.0
72	15.46	16.67	144.35	100.02	1.44	25.0
78	15.78	16.66	139.93	100.02	1.44	25.0
84	15.46	16.67	142.84	99.97	1.40	25.0
90	15.60	16.67	139.94	100.03	1.43	25.0
96	15.74	16.67	141.21	100.02	1.40	25.0
102	15.60	16.67	142.51	100.03	1.41	25.0
108	15.39	16.67	141.20	100.03	1.42	25.0
114	15.38	16.67	139.35	100.02	1.41	25.0
120	15.41	16.67	139.29	100.02	1.39	25.0
126	14.79	16.67	139.54	100.02	1.39	25.0
132	13.99	15.01	133.93	90.03	1.40	25.0
138	13.28	13.33	126.68	79.98	1.49	25.0
144	11.53	11.67	120.21	70.02	1.58	25.0
150	10.55	8.33	104.38	49.98	1.72	25.0
156	9.40	6.67	95.47	40.03	2.09	25.0
162	8.03	5.00	85.11	30.00	2.39	25.0
168	6.31	3.33	72.72	19.99	3.84	25.0
174	6.31	1.67	57.10	10.01	5.64	25.0

Table 3: Viscosity data of Naproxen formulation Gel G3.

higher the speed, the higher the early solvent drag for diffusion and accordingly the agglomeration of micro sponge. It was hypothesized that with the increase in speed, the precipitation of polymer solution droplets gradually became slower, allowing more time for formation of agglomeration. Hence for batch F10 desired porous micro sponges with maximum entrapment of drug was observed.

Particle size analysis of micro sponges

The particle size of the micro sponge was determined by optical microscopy and the micro sponges were found to be uniform in size (Figure 4). The average particle size of all F10 was 110.30 µm the pore size micro sponges could be smaller than 1 µm. Due to smaller pore size bacteria can't penetrate it, which makes self-sterilizing micro sponges.

Morphology determination by scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to determine the Morphology of the prepared micro sponges (Figure 2). SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as 10^{-10} to 10^{-12} grams. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimens. It was observed that the micro sponges were spherical, and uniform with no drug crystals on the surface. The shape of the micro sponges affects the surface area and surface area per unit weight of spherical micro sponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment.

Percentage yield

It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production. After the preparation of formulations the practical yield was calculated as Micro sponges recovered from each preparation in relation to the sum of starting material (theoretical yield). It can be calculated using formula as mentioned in experimental section. The loss of product was due to the formation of some agglomerates and polymer adherence to the container as a result of a viscous nature of slurry. It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production and in this experiment, it is revealed that with increase in polymer ratio with 300rpm, the percent yield also increase (Table 1).

Drug content

The drug content was determined by using phosphate buffer (pH 6.8) with the help of UV-spectrophotometer by dissolving the formulation in phosphate buffer for 12 hrs with continuous stirring and then the samples were filtered using 0.45 µm membrane filter and the samples were analyzed at 230 nm against blank using UV spectrophotometer (Shimadzu, Japan). With this evaluation parameter of Micro sponge it was revealed that the formulation F10 has the Drug content greater i.e. 18.15% with loading capacity 81.56% (Table 1).

Reaction	Microsponge Formulation G3		Commercial Naproxen Gel		Gel Base	
24 hr	1	0	1	0	0	0
48 hr	1	0	1	0	0	0
72 hr	0	0	0	0	0	0

Primary Irritation Index,*PII for G3=0.4 (Negligible Irritant)

Table 4: Score of irritation after application of Microsponge formulation G3, commercial Naproxen gel and gel base.

Sr.no	Time in min	Commercial Naproxen Gel	Microsponge Formulation G3			
			0 month	1 month	2 month	3 month
1	0	0	0	0	0	0
2	30	32.4	29.1	29	28.9	27.50
3	60	40.65	46.41	46.31	45.50	45.52
4	120	68.55	56.78	56.68	56.61	56.45
5	180	78.14	71.65	70.67	70.52	70.06
6	240	89.68	86.95	86.91	86.89	86.79
7	300	93.01	88.96	89.92	88.84	88.49
8	360	96.45	90.90	90.70	90.93	90.00
9	420	96.45	93.89	93.70	93.45	93.40
10	480	96.45	95.75	95.60	95.25	95.00

Table 5: Stability study for microsponge formulation gel G3.

Differential scanning calorimetry (DSC)

Thus, from DSC graph reveals that active ingredient naproxen was entrapped in polymer Eudragit RS-100 and no sharp peak was formed in micro sponges formulation F10 (Figure 3).

pH determination

After getting prepared Micro sponge gel was evaluated for the pH 6.8 ± 0.2 the pH of the gel was determined using digital pH meter of LABINDIA, India. The readings were taken for average of 3 times.

Viscosity measurement

The viscosity of the formulation was analyzed by Brookfield digital viscometer (DV-III+Rheometer) with spindle no 2 at 25°C. This revealed that with prepared formulation gel G3 is pesudoplastic in nature (Table 3).

Drug release studies

In vitro release studies were performed using cellophane membrane using modified apparatus at 37 ± 0.5°C (Table 2). The release medium is selected, while considering solubility of active ingredients to ensure sink conditions. Sample aliquots were withdrawn from the medium and analyzed by the suitable analytical method at regular intervals of time. Cellophane membrane was fitted at the donor side of the cell and predetermined amount of formulation was mounted on the membrane. The receptor medium is continuously stirred at and thermo stated with a circulating jacket. Samples are withdrawn at different time intervals and analyzed using suitable method of assay. In kosmeyer peppas model the formulations mostly having the value of n greater than0.99 ± 0.06 so exhibit super case II transport.

Skin irritation test

Skin irritation test of optimized naproxen loaded microsponge gel (G3) was compared with the marketed and placebo gel. The mean erythemal scores were recorded (ranging from 0 to 4) according to Draize scale and results shows Primary Irritation Index,*PII for G3=0.4 (Negligible Irritant) (Table 4).

Stability study

Stability study were conducted for prepared micro sponge formulation gel G3 as per ICH guidelines, kept at 40 ± 2°C with RH of 45% for a period of 90 days (Table 5). Formulation was evaluated at periodical interval of 1 month for pH, drug content and drug release and formulation found as stable as like commercial naproxen gel.

Conclusion

The micro sponges was prepared by quasi emulsion method and was evaluated for its different parameters which revealed many interesting results for efficient preparation of the micro sponges. The formulation F10 and G3 have better results than other formulations. FT-IR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these 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. 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 topical agents and consists of micro porous beads loaded with active agent. 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. 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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