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"Formulation and Evaluation of Ibuprofen Microsponges for Topical Drug Delivery"

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ABSTRACT
In this study ethyl cellulose facilitated microsponges were prepared by the double emulsification technique (Quasi emulsion technique) and subsequently dispersed in a carbopol gel base for controlled delivery of diclofenac sodium to the skin. The microsponges 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 and Differential scanning electroscopy (DSC). The surface morphology, particle size, production yield, and drug entrapment efficiency of microsponges were examined. Shape and surface morphology of the microsponges were examined using scanning electron microscopy. Particle size of prepared microsponges was observed in the range of 30.80 to102.30 µm. SEM photographs revealed the porous spherical nature of the microsponges in all variations; however, at higher ratios, drug crystals were observed on the microsponges surface. Increase in the drug/polymer ratio (1:0.5 to 1:4.5) increased their yield, the particle size also increased, The pH of the gel was determined having average pH of 7.3 ± 0.4, The viscosity of the formulation was analyzed by Brookfield viscometer with maximum reading of 2874 and minimum reading of 2858 cps, the drug content of different formulations was found in the range 89.9 to 96.05 %, the spreadability of gel containing microsponges revealed in the range of 20.5 to 22.8 gmcm/sec showing good characteristics of spreading, the cumulative release of the formulations are in the range of 76.86-90.06%.

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

I. INTRODUTION

The Skin is one of the areas which have high area for application and use of topical dosage forms. the type of drug and its characteristics are the factors that influence the formulation.

The topical administration is having many advantages, which include the avoid of first pass metabolism. Also, it has more patient compliance for its simple application on the skin without any help of others. The topical administration can be varied to get the type of release and have better advantage of the drug. It can be formulated according to the body conditions and the release can be modified as sustained, controlled release, also can be formulated and make them release to pH activity.

A topical delivery system defined as the substance that carries a specific drug into contact with and through the skin. The challenge to topical drug delivery is the transport across the skin barrier. Topical delivery includes two basic types of product: External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area. Internal topical that are applied to the mucous membrane orally, vaginally or on an rectal tissues for local activity. For the most part topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Although some unintended drug absorption may occur, it is sub therapeutics quantities and generally of minor concern.

Microsponges are polymeric delivery system composed of porous microsponges. They are tiny sponge- like spherical particles with a large porous surface. Moreover, they may enchance stability, reduce side effects and modify drug release favorably. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a noncollapsible structure with a large porous surface through which active ingredient are released in a controlled manner. The size of the microsponge's ranges from 5-300 µm in diameter and a typical 25 µm sphere can have up to 250000 pores and an internal pore

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structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention.

The microsponge Drug Delivery System has advantages over other technologies like microencapsulation and liposomes. Microcapsules cannot usually control the release rate of actives. Once the wall is ruptured the actives contained within microcapsules will be released. Liposome suffers from lower payload, difficult formulation, limited chemical stability and microbial instability.

A microsponge delivery system is patented, highly cross-linked, porous, polymeric microsponges that can entrap wide range of actives and then release them with desired rate. This system is useful for the improvement of performance of topically applied drug. It is a unique technology for the controlled release of topical agents and consists of micro porous beads, typically 10-25 microns in diameter, loaded with active agent. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing of creams, gels, lotions, and powder. Their characteristics feature is the adsorb or load a high degree of active materials into the particle and on to its surface.

II. MATERIALS AND METHODS

Ibuprofen drug got gift sample from Karnataka antibiotics and Pharmaceutical limited. Bangalore, polymer such as ethyl cellulose, poly vinyl alcohol from Research lab fine chem industries , Dichloromethane, Glycerol, Carbopol 934, Triethanol amine, Methlyl paraben, Propyl paraben.

FORMULATION OF IBUPROFEN MICROSPONGES

The microsponges containing the anti inflammatory and Antipyretic drug Ibuprofen , as the core material were prepared by Quasi emulsion method. Here, the combinations of Drug and Polymers at various ratios were added to 10 ml of organic solvent (dicholoromethane) kept under magnetic stirrer for about 15 mins, to form a uniform polymer solution.This solution was slowly poured into the dispersion medium containing 100 ml of 0.5 % of PVA solution and 1 ml of glycerol. The whole system was stirred at constant speed with a mechanical stirrer equipped with a three-blade propeller at room temperature and Stirring was continued over 2-3 h.

After completion of stirring, the formed microsponges are separated by filtration through Whatman filter paper and air dried for 48 h.

Table 1:-Formulation of Ibuprofen Microsponges:-

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ibuprofen (gm)	1	1	1	1	1	1	1	1	1
Ethyl cellulose(gm)	0.5	1	1.5	2	2.5	3	3.5	4	4.5
PVA (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dichloromethane (ml)	10	10	10	10	10	10	10	10	10
Glycerol (ml)	1	1	1	1	1	1	1	1	1
Distil Water (ml)	100	100	100	100	100	100	100	100	100
Drug : Polymer	1:0.5	1:1	1:1.5	1:2	1:2.5	1:3	1:3.5	1:4	1:4.5

FORMULATION OF GEL CONTAINING IBUPROFEN MICROSPONGES

Table 2: Formulation for topical gel

Sl.no	Ingredients	Quantity (mg/ml)
01	Ibuprofen microsponges	5%
02	Carbopol 934	35
03	Triethanolamine	2
04	Methyl paraben	3

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05	**Propyl paraben**	**1**
06	**Distilled water**	**q.s**

PROCEDURE

1. A clear dispersion of carbopol (35 mg) is prepared in water (q.s) using moderate agitation.
2.Triethanolamine (1-2 drops) is used to neutralise the formulation and subsequently preservatives Methyl paraben (3 mg) and Propyl paraben (1 mg) was added to resist the microbial growth.
3. And then volume was maintained with water. Gel prepared were degassed with ultrasonication.

EVALUATION OF IBUPROFEN MICROSPONGES:

PERCENTAGE YIELD

The prepared microsponges were collected and weighed from different formulations. The actual weight of the microsponges was divided by the total weight of the drug and polymer which were used for the preparation of the microsponges.

The percentage yield was calculated using the following formula:

% YIELD= (Actual weight of microsponges / Total weight of Drug & Polymer) X 100

DRUG ENTRAPMENT EFFICIENCY

The microsponges equivalent to 100 mg of Ibuprofen from all batches were accurately weighed and crushed. The powdered of microsponges placed in 100 ml volumetric flask and add pH 7.4 phosphate buffer make up to the mark and filtered through Whatman filter paper No.44 After filtration, from this solution accurate quantity (1ml) was taken and diluted up to 10ml with add pH 7.4 phosphate buffer. From this solution accurate volume (1ml) was pipette out and diluted up to 10ml with add pH 7.4 phosphate buffer.The absorbance was measured at 264 nm.

The drug entrapment efficiency was calculated using the following formula:

%Drug Entrapment Efficiency=(Practical drug content/Theoretical drug content)X100

PARTICLE SIZE ANALYSIS

Particle size of the prepared microsponges was determined by optical microscopy. The optical microsponges was fitted with an ocular micrometer and a stage micrometer. The eyepiece micrometer was calibrated. The diameters of particles of more than 200 microsponges were measured randomly by optical microscope**.**

Calibration of eyepiece micrometer:

One division of the stage micrometer = 0.01 mm = 10 µm

∴µ=(SM/EM) × 10

Where, µ- correction factor

SM- Reading of stage micrometer which coincides with reading of eyepiece micrometer (EM).

SHAPE AND SURFACE MORPHOLOGY

The shape and surface characteristics of the prepared microsponges were evaluated by means of scanning electron microscopy. The samples for scanning electron microscopy were prepared by gently sprinkling the microsponges on a double adhesive tape, which is sticked to an aluminum stub. The stubs were then coated with gold using a sputter coater under high vacuum and high voltage to achieve a film thickness of 30 nm. The samples were than imaged using a 20 KV electron beam.

EVALUATION OF IBUPROFEN MICROSPONGES GEL

Visual inspection

The organoleptic properties, such as color, texture, consistency, homogeneity, and physical appearance of gel containing microsponges were checked by visual observation.

pH measurement

Gel formulation pH was recorded using digital pH meter. 5 g gel was dispersed in 45 ml distilled water at 27° C and solution pH was measured.

Spreadability studies

One of the requisite qualities for an ideal gel is to pursue excellent spreadability. Spreadability is used to express the extent of the area of skin or affected part to which gel readily spreads. A spreading value significantly affects therapeutic efficacy of the formulation. Expression of spreadability is given in terms of time (in seconds) taken by two slides to slip off from gel placed in between under application of specific load. Better spreadability is indicated by minimum time required for slides separation. Mathematical expression used for spreadability calculation was:

$$S = \frac{ML}{T}$$

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Where, M = weight (in gm) attached to upper slide, L = length (in cm) of glass slides, T = time (in sec) taken to separate the slides.

Viscosity Measurement

The viscosity of the gel formulation was measured with a Brookfield viscometer with spindle number 7 at 50 rpm . An average of three readings was used to calculate viscosity.

In-vitro drug diffusion studies

Diffusion studies were carried out for all the formulation. In-vitro release was performed using France difusion cell apparatus at 37 ^{0}C. The release medium is selected while considering of active ingredients to enure sink condition. Sample were withdrawn from the medium and analyzed by the suitable analytical method at regular intervals of time. Egg membrane was fitted at the donar site of the cell and predetermined amount of formulation was mounted on the membrane. The sample withdrawn at different time intervals and analyzed using suitable method of assay.

In-vitro drug release kinetics

The cumulative amount of Ibuprofen release at different time intervals from the different formulation of microsponges were fitted to zero order kinetics, first order kinetics, Hixson-Crowell Kinetics, Higuchi's model and Korsmeyer-Peppas model to characterize mechanism of drug release.

Stability studies

Stability of a drug can be defined as the ability of a particular formulation, in a specific container to remain within its physical, chemical, therapeutic and toxicological specifications or as the time from the date of manufacture and the packing of formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristic have not changed appreciably.

Method

The optimized formulation was subjected for stability studies over a period of 3 months. The microsponges were packed in amber colored screw capped and kept for the stability at room temperature. Samples were taken after 3 months analyzed for the drug content, %Drug Entrapment Efficiency, change in appearance, pH, In-vitro diffusion profile. In-vitro drug release at 0 month and after 3 months of stability study was compared.

III. RESULTS AND DISCUSSION

COMPATIBILTY STUDIES

FOURIER TRANSFORM INFRARED SPECTROSCOPY

Drug polymer compatibility studies were carried out using Fourier Transform Infrared spectroscopy to establish any possible interaction of Ibuprofen with the Ethyl cellulose and polyvinyl alcohol Polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug. The results indicated that the principle peaks obtained from the combinations were almost similar to that of pure drug without any significant change in their position, indicating no chemical interaction between (drug) Ibuprofen and (polymers) Ethyl cellulose and polyvinyl alcohol. The FTIR spectra of pure drug and polymers shown in Figure 01 and 02.

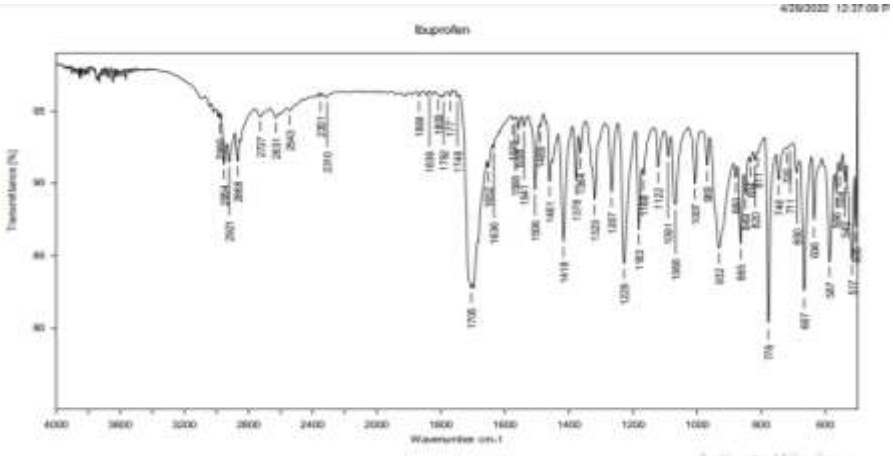

Figure 01: FT-IR Spectra of Ibuprofen

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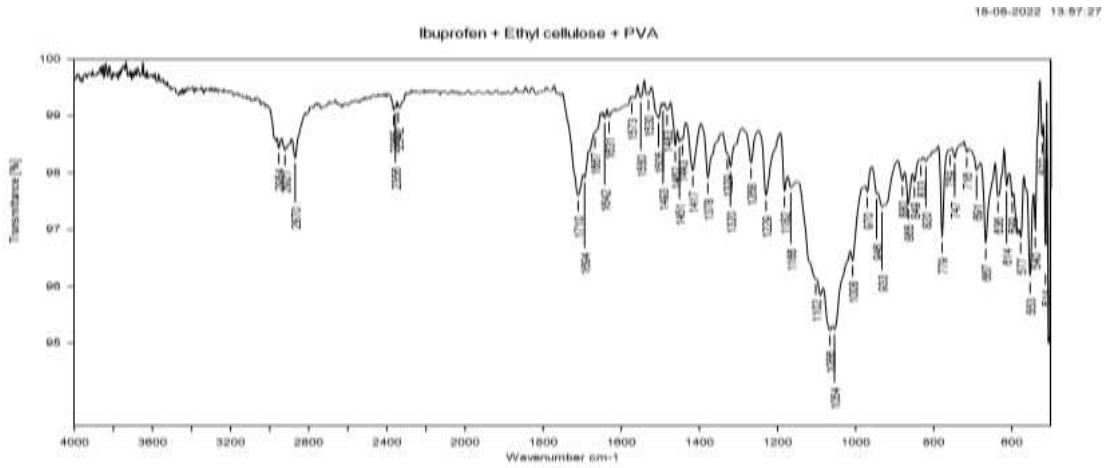

Figure 02: FT- IR spectra of Ibuprrofen + Ethyle cellulose +Polyvinyl alcohol

DIFFERENTIAL SCANNING CALORIMETRY (DSE)

Thermal behavior of Ibuprofen, ethyle cellulose and polyvinyl alcohol were studied with the help of DSC. The thermogram obtained are shown in **Figure 03 and 04**. Drug has shown sharp endothermic peak at 78.17^{0}C corresponding to its melting point. The ethyle cellulose and polyvinyl alcohol has also shown near 255.44^{0}C and 185.11^{0}C. Therefore, Ibuprofen appeared in the physical mixture indicating that there was no possible interaction between the drug and the excipients in the formulation.

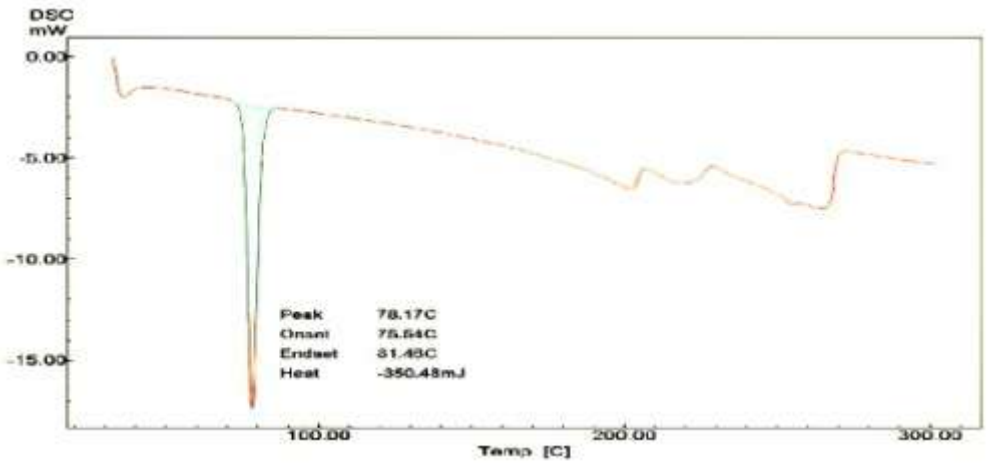

Figure 03: DSC thermogram of Ibuprofen

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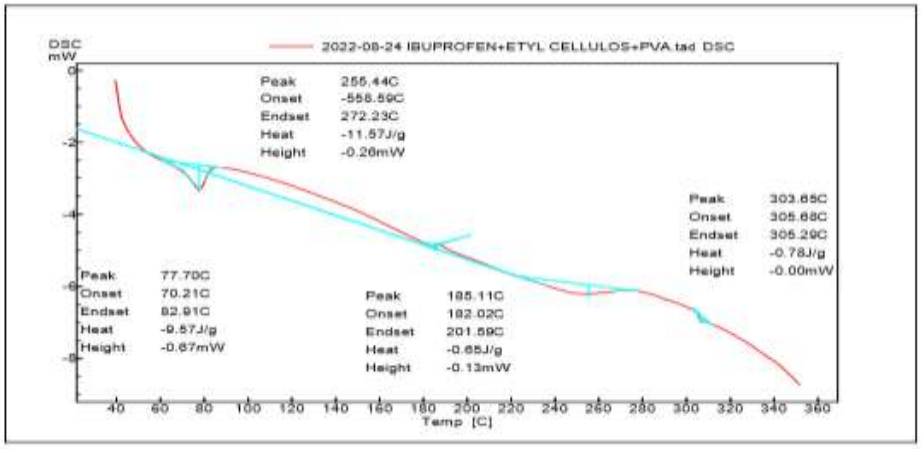

Figure 04: DSC thermogram of Ibuprrofen + Ethyl cellulose + Polyvinyl alcohol

EVALUATION AND CHARACTERIZATION OF THE PREPARED MICROSPONGES

PERCENTAGE YIELD

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to formation of agglomerates and polymer adherence to the container as a result of a viscouis nature of slurry. The percentage yield was found to be in the range of 70.06% to 80.46%. The percentage yield of the prepared Microsponges is recorded in **Table 03.**

Table 03: Percentage yield of Ibuprofen microsponges

Formulation Code	Drug: Polymer Ratio	%Yield
F1	1:0.5	70.06± 1.08
F2	1:1	73.70±0.84
F3	1:1.5	73.52±0.12
F4	1:2	71.30±0.43
F5	1:2.5	71.80±0.39
F6	1:3	76.20±0.54
F7	1:3.5	79.50±0.21
F8	1:4	80.40±0.12
F9	1:4.5	80.01±0.67

DRUG ENTRAPMENT EFFICIENCY

The % of drug entrapment efficiency of all the formulations was in the range of 36.4 % to 71.05%. The % drug entrapment efficiency of the prepared microsponges is displayed in **Table 04.** The drug entrapment efficiency of the prepared microsponges decreases progressively with an increase in proportion of the polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in lowers entrapment efficiency. Similarly increasing ethyle cellulose ratio shows decreased entrapment efficiency of Microsponges. This may be attribute increased ethyl cellulose proportion that results in reduced drug diffusion into the microsponges. Entrapment efficiency was decreased upon increasing polymer composition.

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Table 04: Percent Drug Entrapment efficiency of Ibuprofen microsponges

Formulation Codes	%Drug Entrapment Efficiency
F1	45.39±0.12
F2	46.60 ±0.49
F3	51.40 ±0.44
F4	71.05 ±0.30
F5	69.90 ±0.26
F6	64.80 ±0.15
F7	59.30 ±0.32
F8	47.00 ±065
F9	36.40 ±0.26

PARTICLE SIZE ANALYSIS

The prepared microsponges were in a size range suitable for topical delivery. The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased emulsion droplet size and finally a higher microsponge size. Ibuprofen microsponge had a size range of 30.80 to102.30 µm. The particle size data is presented in **Table 05**. It is interesting to note that the increase in particle size is comparable with the decrease in entrapment efficiency. Higher concentration of polymer in the sample leads to an increased frequency of collision resulting in fusion of semi formed and producing an overall increase in the particle size.

The particle size distribution of Microsponges obtained depends on the size of the droplets, as well as stirring speed. Increasing the dispersive force also decreased microsponge mean diameter. Mean size decreased at higher rotational speeds, thus, an optimal impeller rotational speed was chosen to prepare small microsponges with a narrow size distribution suitable for topical drug delivery.

Table 05: Particle Size data of Formulations F-1 to F-9

Formulation Codes	Particle Size (µm)
F1	30.80±0.36
F2	42.60±0.47
F3	63.40±0.25
F4	79.50±0.65
F5	81.70±0.27
F6	60.40±0.86
F7	63.70±0.13
F8	74.40±0.18
F9	102.30±0.56

SHAPE AND SURFACE MORPHOLOGY

Morphology of the Microsponges was investigated by Scanning electron microscopy (SEM). The photographs of the optimized formulations taken by scanning electron microscope are shown in the **Figure 05.**

The results of SEM (Figure: 14) revealed that the Microsponges were discrete and spherical in shape with a rough outer surface morphology which might be due to surface associated drug. Surface topography of optimized formulation was carried out. SEM study showed that pores were

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found on the surface of microsponges which indicates that drug is released by diffusion mechanism.

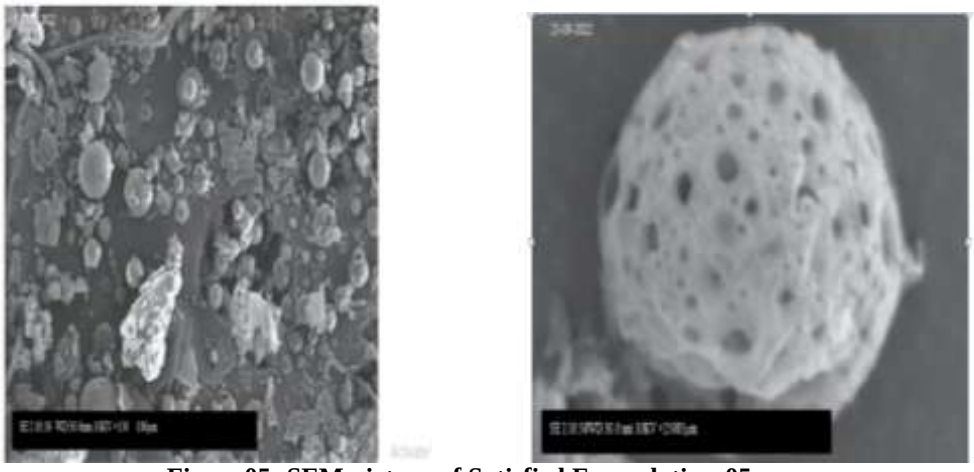

Figure 05: SEM picture of Satisfied Formulation-05

EVALUATION OF IBUPROFEN MICROSPONGES GEL

pH

The pH of the prepared microsponges gel was measured using digital pH meter (pH by Hanna). The pH of formulation was found to be within the range 7.06 to 7.40 respectively.The pH data represented in **Table 06.**

Table 06: pH data formulation F1 to F9

Formulation	Average
F1	7.06±0.05
F2	7.10±0.05
F3	7.20±0.00
F4	7.16±0.05
F5	7.23±0.05
F6	7.30±0.05
F7	7.20±0.10
F8	7.26±0.11
F9	7.40±0.11

Spreadability

Spreadability can be determined by glass slides and wooden block which was provided by a pulley at one end. The Spreadability of formulations was found to be 20.5 to 22.8 gmcm/sec respectively. The spreadability data represented in **Table 07.**

Table 07: Spreadability data formulation F1 to F9

Spreadability (gcm/sec)	Average
F1	**22.1±0.28**
F2	**21.6±0.28**
F3	**22.3±0.28**
F4	**22.6±0.28**
F5	**22.8±0.28**
F6	**21.6±0.28**
F7	**21.3±0.28**
F8	**20.5±0.50**
F9	**20.5±0.50**

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Viscosity

The viscosity of different microsponges were determined using a Brookfield digital rheometer with spindle number 7 at 50 rpm. The viscosity of formulation was found to be 2688 to 2858 cps respectively. The viscosity data represented in **Table 08** which revealed that with increase in polymer concentration the viscosity also increases.

Table 08: Viscosity data formulation F1 to F9

Formulation	Average(cps)
F1	2794.3±9.03
F2	2858.3±14.64
F3	2843.6±6.42
F4	2750.6±8.62
F5	2853.3±5.89
F6	2746.6±8.02
F7	2751±12.00
F8	2688.6±8.08
F9	2733±11.26

Drug content of microsponge gel

Drug content can be determined by dissolving 100 mg of the gel in phosphate buffer pH 7.4 for 24 h, filter and then suitably dilute and measure for the absorbance at λmax 264 nm. Drug content was determined for the prepared gel formulations was found to be 89.9 to 96.05 %. The drug content data represented in **Table 09** drug content is decreasing with increase in content of polymer due to improper carrying of drug by the polymer.

Table 09: Drug content of 5% Ibuprofen microsponge gel

Formulation	Drug content (%)
F1	93.68±0.23
F2	96.05±0.22
F3	96.0±0.18
F4	94.7±0.24
F5	94.2±0.30
F6	93.4±0.09
F7	92.6±0.16
F8	90.7±0.12
F9	89.9±0.28

IN-VITRO DRUG DIFFUSION STUDIES

In-vitro drug release of Ibuprofen microsponges gel was performed by diffusion method. Activated egg membrane was used as membrane between donor compartment and receptor compartment. The receptor compartment was filled with phosphate buffer pH 7.4. The best drug release of 88.18% was showed by formulation F5.

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Table 10: In-vitro Drug Diffusion data of F1 to F9 Formulations

Time(h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	8.95±1.02	8.1±0.43	7.52±0.45	7.81±0.03	8.32±0.10	7.91±0.43	7.32±0.15	6.79±0.25	6.23±0.40
2	17.92±1.23	15.51±0.32	14.83±0.63	16.64±0.42	17.68±0.35	14.53±0.25	16.54±0.12	13.87±0.43	12.83±0.45
3	31.49±0.23	29.34±1.32	32.41±0.32	29.79±0.82	30.54±1.02	27.17±0.20	28.72±0.15	26.31±0.30	25.07±0.50
4	42.67±1.01	40.12±1.52	39.93±0.97	38.05±0.88	40.23±0.13	37.09±0.43	38.60±0.52	36.21±0.43	34.78±0.13
5	50.33±2.17	48.67±0.98	46.72±1.45	47.16±1.04	49.78±0.50	44.32±1.53	46.86±2.62	45.89±0.12	43.42±0.14
6	58.85±3.01	55.32±3.63	57.31±0.32	58.12±0.53	56.53±0.53	55.43±1.01	54.34±0.33	52.76±0.52	53.47±0.18
7	65.31±3.12	63.83±2.50	64.03±1.01	63.48±1.40	65.21±1.40	62.32±1.43	61.14±0.52	59.56±0.20	57.83±0.08
8	74.65±4.20	73.15±2.32	72.75±1.13	71.02±1.59	73.16±1.52	70.18±0.63	68.27±1.24	69.45±0.71	66.11±0.30
9	82.41±2.45	83.21±3.59	80.34±1.56	81.16±2.65	80.74±1.02	78.09±1.11	76.48±0.25	73.86±0.76	72.54±0.13
10	90.6±1.54	88.29±1.5	87.47±2.10	86.21±1.8	89.18±1.40	86.78±2.32	82.18±2.33	79.52±0.35	76.86±0.23

IN-VITRO DRUG RELEASE KINETICS

The data obtained from in-vitro diffusion studies were fitted in different models viz. zero order, first order, Higuchi and Korsemeyer- Peppas equation. It was observed that the highest correlation of best formulation F5 was found for Higuchi model(R^2=0.898).The n value found to be more than 0.5 which indicates the drug release would be by Fickian diffusion.

STABILITY STUDIES

From the stability studies, it was clear that the formulation were physically and chemically stable for 90 days. And there was no significant change in the physical parameters, drug content and in-vitro diffusion profiles.

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Table 11: Stability study of F5 formulation at room temperature

EVALUATION OF SATISFIED F5	RESULTS	
	0^{th} day	**90^{th} day**
pH	7.23±0.05	7.2±0.06
Viscosity(cps)	2853±5.89	2839± 4.38
Spreadabality (gm cm s^{-1})	22.8±0.28	22.6 ±0.35
Drug content (%)	94.2±0.30	94.12 ±0.58

IV. CONCLUSION

In the present work, microsponges were formulated to deliver Ibuprofen via topical route. Details regarding the preparation and evaluation of the formulations have been discussed in the previous chapters. From the study following conclusions could be drawn:

- The results of this investigation indicate that quasi emulsion technique can be successfully employed to fabricate Ibuprofen -loaded microsponges.
- FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers used.
- Micromeritic studies revealed that the mean particle size of the prepared microsponges was in the size range of 30.80 to102.30 µm and are suitable for topical administration.
- Increase in the polymer concentration led to an increase in % yield and particle size of the microsponges.
- The % drug entrapment efficiency decreased with increasing the polymer concentration and also the formulations containing high ethyl cellulose proportion shows good entrapment efficiency.
- SEM analysis of the microsponges revealed that all the prepared microsponges were discrete, spherical in shape and had ideal surface morphology.
- The pH of prepared microsponges was found to be 7.06 – 7.40 and are suitable for topical administration.
- The spreadabality of prepared microsponges was found to be 20.5 – 22.8 gmcm/sec and are suitable for topical administration.
- The viscosity of prepared microsponges was found to be 2688 – 2858 cps and are suitable for topical administration.
- The drug content of gel formulation of prepared microsponges was found to be 89.9 – 96.05% and are suitable for topical administration.
- The in-vitro study demonstrated that formulations F5 containing ethyl cellulose proportion and formulation containing small particle size with the acceptable size as evidenced by the percentage of particles at the end of 10 h than compared with rest of the formulation.
- The in-vitro drug diffusion decreased with increase in the polymer concentration. The drug diffusion was characterized by an initial phase of higher release followed by a second phase of moderate release.
- The formulation F5 containing ethyl cellulose showed the 88.18 % of drug release within 10 hours so it is consider as best formulation.
- The formulation F5 was selected for stability studies on the basis of their better and satisfactory evaluation studies parameter. Results showed there was not much variation in physical parameters even after the period of 90 days.
- From the results obtained it was concluded that, formulations F5 containing ethyl cellulose ratio 1:2.5 are found to be stable and retained their original properties during their study period.

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