Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(3), 1700-1711 | ISSN:2251-6727

Formulation and Development of Microsponges Loaded Topical Formulation Containing Non Steroidal Anti-Inflammatory Drug

Bornare Ashwini*, Dr. Karodi Revan[2], Dr. Nikam Sarika[3], Mali Mahesh[4], Dahake Vaishnavi[5]

*Department of pharmaceutical chemistry, Dr. D. Y. Patil college of pharmacy, Akurdi,Pune

[2]Associate Professor at Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune

[3]Associate Professor at Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune

[4]Department of pharmaceutical chemistry, Dr. D. Y. Patil college of pharmacy, Akurdi, Pune

[5]Department of pharmaceutical chemistry, Dr. D. Y. Patil college of pharmacy, Akurdi, Pune

(Received: 04 February 2024 Revised: 11 March 2024 Accepted: 08 April 2024)

KEYWORDS

Microsponges,

Quasi emulsion method,

Controlled release,

Topical preparation

ABSTRACT:

Introduction: Arthritis is a chronic inflammatory condition affecting millions worldwide, leading to extreme pain and inflammation. Available therapies include surgery, laser, and drug treatments like corticosteroids and methotrexate. However, these drugs often cause itching, redness, and heart-related issues. Celecoxib, a COX-2 inhibitor, is used to block inflammation and pain. Microsponge Drug Delivery Systems offer advantages over other technologies like microencapsulation and liposomes, improving solubility of poorly water-soluble drugs like celecoxib. These microsponges are converted into a cream formulation to enhance applicability and patient compliance.

Objectives: The objective was to prepare and assess creams with celecoxib microsponges, a nonsteroidal anti-inflammatory drug for arthritis symptoms. We used the quasi-emulsion solvent diffusion method with Eudragit RS-100 to prepare microsponges with different drug-polymer ratios.

Methods: Drug-loaded microsponges were prepared using the Quasi-emulsion solvent diffusion method. Initially, Eudragit RS 100 was dissolved in dichloromethane, followed by drug addition and ultrasonication at 35°C. This inner phase was then mixed with an outer phase containing polyvinyl alcohol, stirred, and left to form rigid microsponges through solvent evaporation. After filtration, washing, and drying, microsponges were obtained. Key variables were optimized using factorial design. Creams were prepared via oil-in-water emulsion, with heating of aqueous and oil phases over a water bath.

Results: The results confirmed that celecoxib microsponges significantly increased solubility and met all required limits. Celecoxib-loaded microsponges, formulated with Eudragit RS100, achieved high production yield and drug content. This formulation exhibited prolonged drug release.

Fourier transform infrared and differential scanning calorimetry studies were carried out for pure celecoxib and microsponges

Conclusions: Polymer-based microsponge delivery systems, developed via quasi-emulsion solvent diffusion, offer controlled release of celecoxib. These systems aim to reduce application frequency, hypersensitivity reactions, and improve bioavailability. Creams containing microsponges provide prolonged drug release, promising relief for arthritis symptoms.

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JCHR (2024) 14(3), 1700-1711 | ISSN:2251-6727

1. Introduction

Arthritis is a chronic inflammatory condition affecting millions worldwide, necessitating long-term management strategies. [1] There are different types of arthritis like rheumatoid arthritis, osteoarthritis, Psoriatic arthritis, and because of this all types patients suffer from extreme pain and inflammation. arthritis is an autoimmune disease. autoimmune disease means our own cells specifically our joint cells make antibodies against them and because of this pain and inflammation are occur. Currently available therapies for arthritis are surgery, laser and psoralen and ultraviolet (UV) B phototherapy, [2] available drugs are corticosteroid, methotrexate, sulfasalazine. [3] The disadvantages of these drugs are the itching, redness, heart related problem. Celecoxib is cyclooxygenase 2 (COX-2) specific inhibiting agent that inhibits the conversion of arachidonic acid to prostaglandin that mediate pain and inflammation. [4] Celecoxib is a selective COX-2 inhibitors they might block inflammation, pain, and fever. When blocking cox at that time we consider that we mainly block cox2 because we avoid pain and inflammation and if we use medication that also block cox1 then it is not beneficial because cox1 regulates the acid production when drug blocks the cox1 the acid production will get disturb and increase the acid production. The Microsponge Drug Delivery System has advantages over other technologies like microencapsulation and liposomes. [5] 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. 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. [6] Cream refer to disperse system, in which one insoluble phase is dispersed as droplets in a second liquid. Cream are often preferred over other topical preparation because they are less irritating and easy to apply Eudragit RS 100 is used as a polymer for improving solubility. These microsponges are prepared to increase solubility of the drug which is poorly water soluble. [7] To enhance applicability and improve patient compliance, the drug-loaded microsponges are transformed into a cream formulation.

2. Methods

- Material –

Material – Materials for the current project were obtained from several sources.

Celecoxib was provided as a gift sample, other polymer and all ingredients were provided by college. he remaining substances were of analytical quality.

- Method [8,9,10]

Characterization of pure drug

1) Melting point

Melting point of celecoxib was noted. In a capillary tube having one end closed, sample was inserted. Then capillary was inserted in bath of silicone oil which was heated in controlled manner with the help of electric heating coil. The temperature at which drug sample started melting was noted as melting point temperature

2) Differential scanning calorimetry (DSC)

To evaluate thermal behavior and thermotropic characteristics of drug, DSC study was implied. It is based on principle of measuring heat flow in and out of sample and reference for the period of controlled temperature cycle.

3) FTIR

To check purity of drug and excipients, FTIR spectra were recorded (FTIR, A-410, Jasco, Japan) over wavelength range of 4000–400 cm^{-1} at resolution of 4 cm^{-1}. Samples were dispersed in KBr and compressed in pellets by applying 5 tons pressure for 5 min using hydraulic press. Formed pellets were kept in light path and spectra were recorded.

4) UV

Calibration curve in pH 7.4 phosphate buffer From the standard solution, a stock solution was prepared to give a concentration of 100 µg/ml in 7.4 buffer. Aliquots of 0.5, 1.0, 1.5, 2.0, and 2.5 ml from the stock solution were pipetted out into 10 ml volumetric flasks. The volume was made up to the mark with 7.4 buffer. These dilutions gave 5, 10, 15, 20, and 25 µg/ml concentration of celecoxib, respectively. The absorbance of prepared solutions of celecoxib in 7.4 buffer was measured at 252 nm spectrophotometrically against 7.4 buffer blank. Standard plot data of celecoxib in 7.4 pH buffer are reported.

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JCHR (2024) 14(3), 1700-1711 | ISSN:2251-6727

PREPARATION OF MICROSPONGES

TABLE 1: PREPARATION OF MICROSPONGES

Batches	Drug (mg)	Eudragit (mg)	Dichloromethane: Methanol (1:1 ml)	Polyvinyl alcohol (mg)	Distilled water (ml)
1	100	100	5	500	50
2	100	100	10	500	50
3	100	100	5	500	50
4	100	200	10	500	50
5	100	200	5	500	50
6	100	200	5	500	50
7	100	250	10	500	50
8	100	250	5	500	50
9	100	250	5	500	50

The drug-loaded microsponges were fabricated using the Quasi-emulsion solvent diffusion method. Firstly, the inner phase was prepared by dissolving Eudragit RS 100 in dichloromethane solvent, followed by the addition of the drug and ultrasonication at 35°C. Subsequently, this inner phase was combined with the outer phase containing polyvinyl alcohol and stirred at 800-900 rpm for 2 hours, allowing for the formation of desired rigid microsponges through organic solvent evaporation. The resultant rigid microsponges were filtered, washed with distilled water, and then dried. Key process variables such as Eudragit RS 100 and Polyvinyl alcohol were optimized using 3^2 factorial design techniques. [10]

EVALUATION OF MICROSPONGES

Physical Appearance

The organoleptic properties of the microsponges, like color, odor and physical appearance was checked by visual observation.

Determination of Production Yield (PY)

Polymer and drug accurately weighed and then after preparation and drying of the microsponges, weight of microsponges was taken. Production yield was calculated from the following formula. [11]

$$\mathbf{PY(\%)} = \frac{\textbf{Practical mass (Microsponges)}}{\textbf{Therotical mass (Polymer + Drug)}} \times \mathbf{100}$$

Actual Drug Content and Loading Efficiency

1. Actual drug content

Weighed a specific amount of microsponges containing the drug. Extracted the drug from the microsponges by sonication. Measured the concentration of the drug in the solution using suitable UV spectrometry.

By determining the drug content in the weighed quantity of microsponges, the actual drug content was found using the following formula. [12]

$$\textbf{Actual drug content \%} = \frac{\textbf{Mact}}{\textbf{Mms}}$$

Mact –actual drug content in weighed quantity of microsponges

Mms –weighed quantity of powder of microsponges that taken for analysis

2. Loading efficiency (%)

$$\textbf{Loading efficiency (\%)} = \frac{\textbf{Mact}}{\textbf{Mthe}}$$

Mthe –theoretical amount of drug in microsponges calculated from quantity added

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Particle Size Analysis of Microsponges

Determination of mean average particle size of celecoxib microsponges was carried out by using optical microscopy. A minute quantity of microsponges was spread on a clean glass slide and viewed under microscope. At the resolution of 100x and 40x to determine sphericity and size of the microsponges, study the aggregation of microsponges, unreacted particles and segregation of material measured by an image analysis system.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) is an electron optical imaging technique that photographic images and elemental information. The signals that derive from interactions reveal information about the sample including external (texture), chemical composition, and crystalline structure and orientation of materials making up the sample. Used to determine particle size distribution, surface topography, texture and examine the morphology of fractured or sectioned surface. Prepared microsponges were coated with platinum under sputter coater an argon atmosphere at room temperature and then microsponges were examined with a (NOVA NanoSEM) operating at 15Kv. [13]

Infrared Analysis

The FTIR spectra are used to identify the drug and help to detect the interaction of drug with polymers. FTIR spectrum of pure drug and physical mixture of drug with polymers stained on FTIR (Shimadzu 4100) instrument. The procedure consisted of dispersing sample in excess of potassium bromide nearly at the ratio 1:100, mixed well and then mixture kept into sample holder for analysis. The spectrum of pure drug and potassium bromide (1:100) was taken. The spectrum of microsponge optimized batch with potassium bromide (1:100) was taken. [14]

Powder X-ray Diffraction Analysis (PXRD)

The average spacing between layers or rows of atoms were measured and the orientation of a single crystal or grain was determined. Then the crystal structure of an unknown material was found, the size, shape and internal stress of small crystalline regions were measured. To obtain the changes in the crystallinity of the microsponges prepared, the PXRD study was carried out by using X ray diffractometer (Bruker AXS, Germany) powdered product samples were scanned between 2°-100° 2Ɵ at a scan speed of 0.1 2Ɵ/sec using 1.524 Å radiations. [15] The PXRD patterns were recorded and analyzed. For this the samples of pure drug, prepared batch and physical mixture of the same batch was taken and observed.

Differential Scanning Calorimeter Analysis

The enthalpy of melting (fusion) and the heat capacity, glass transition temperature, and the change in heat capacity for the glass transition were determine Differential scanning calorimetry (DSC) monitors heat effects associated with phase transitions and chemical reactions as a function of temperature. In a DSC the difference in heat flow to the sample and a reference at the same temperature, is recorded as a function of temperature. Thermograms of pure celecoxib, celecoxib microsponges formulation and celecoxib cream were obtained using DSC.

PREPARATION OF CREAM

The cream consisting of microsponges containing celecoxib, emulsifier tween 80, liquid paraffin as an emollient, cetostearyl alcohol as a viscosity increasing agent, humectant glycerine. Cream were prepared by oil in water emulsion method. [16] the heat was used for heating the aqueous and oil phases over a water bath in a beaker. Tween-80, Cetostearyl Alcohol, cocoa butter, and Liquid Paraffin was comprised in oil phase. Glycerin, De-ionized water and Triethanolamine was composed in the aqueous phase. In the beginning, the speed was at homogenizer at 2000 rpm for 20 min, with continuous stirring aqueous phase Dropwise added to the oil phase. After 20 min the speed was decreased to 1000 rpm of the homogenizer for a further 5-10 min. the speed of homogenization was further reduced to 500 rpm during the last extended 5 min. in the process has resulted in the formulation of celecoxib cream.

Figure 1: Prepared cream formulation

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JCHR (2024) 14(3), 1700-1711 | ISSN:2251-6727

TABLE 2: PREPARATION OF CREAM OF MICROSPONGES

Ingredient	category	F1	F2	F3	F4	F5	F6	F7	F8	F9
Celecoxib microsponges (mg)	API	100	100	100	100	100	100	100	100	100
Tween 80(ml)	emulsifier	2	1	1	1	1	2	1.5	1.5	2
Liquid paraffin(ml)	emollient	1.25	3	2.5	2.5	2	2	1.5	2.3	2
Cetostearyl alcohol(gm)	Viscosity modifier	1	1	1	1	1	1	1.5	2	1
Cocoa butter	base	2	-	1.5	1	1.7	1	1.3	1	1
Stearic acid	Emollient as well as base	1	1.6	2	1.9	2	2.5	2	1.6	2
glycerin	humectant	2.5	2.5	2.5	2.5	3	4	4	4	4
triethanolamine	stabilizer	2	2	2	2	1.5	1.5	1.5	1.5	1.5
Methyl paraben	preservative	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Purified water	vehicle	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

EVALUATION OF CREAM

1. Organoleptic properties.

a. color

b. homogeneity

2. Consistency.

3. pH.

4. Particle size of Cream.

5. Spreadability.

6. Viscosity.

7. Drug content.

8. In vitro drug release study.

9. Stability Study.

10. In vitro Anti-inflammatory activity (Protein denaturation method)

Physical examination: The prepared topical cream was inspected visually for their colour, homogeneity, consistency and appearance.

Colour: The colour of the formulation was checked against white and black background.

Consistency**:** The consistency was checked by applying on skin.

Determination of viscosity: Viscosity measurement was carried out by using Brookfield viscometer. Sufficient sample was placed in a cylindrical tube and measured the reading at 37˚C ± 2°C and rotating the spindle no. 7.

Determination of pH

For measurement of pH in the formulation of Celecoxib cream Digital pH meter was used. The pH buffer solution was used for calibration. [17]

Spreadability

The spread ability experiment was accomplished by two glass slides. A cream is sandwiched in between these glass slides. In this procedure 1g formulation was kept above the first glass slide and 10g was kept on the second slide until no further probable spreading. The diameter of escalated circle was measured and defined as spread ability proportional values.

The spreadability was then calculated using the following formula

S= M×L/T

Where, S= spreadability, M= weight placed on the upper slide, L= length moved by the glass slide, T= time

Accelerated stability studies:

The prepared celecoxib microspongic cream were packed in aluminum collapsible tube (5 g) and subjected

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JCHR (2024) 14(3), 1700-1711 | ISSN:2251-6727

to stability studies at 5°C/60 % RH, and 40°C/ 75 % RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties, drug content, and drug release profiles

In vitro diffusion studies procedure

Franz diffusion cell apparatus was used to perform the procedure. The dialysis cellulose membrane has a 11 ml compartment between receptor and donor and held in the Franz diffusion cell apparatus. The receptor compartment chambers were filled with 11 ml pH 7.4 phosphate buffer and Celecoxib cream was used and the cream. During the experiment the solvent temperature was stable at 37 °C The procedure was continued for 8 Hrs with the gap at 0.5, 1, 1.5, 2, 3, 4, 8 h. From the cell receptor compartment, 1.0 ml sample was drawn out at predetermined time and immediately fill up with the same volume of buffer at 37 °C [18]. The withdrawn samples were filtered and the Celecoxib absorption was measured at 250 nm UV-visible spectrophotometer.

RESULT AND DISCUSSION

DRUG IDENTIFICATION

Melting point

The reported melting point of celecoxib is in the range of 161-164°c. The observed melting point ranged between 160-163°c.

Spectroscopic studies

EVALUATION OF MICROSPONGES

Determination of production yield

TABLE 3: PRODUCTION YIELD(%)

Batch Code	Celecoxib:Eudragit	Volume of inner phase solvent(Dicholoromethane:methanol)	Production yield (%)
1	01:01	5	70
2	01:01	10	78
3	01:01	5	70
4	01:02	10	71
5	01:02	5	80
6	01:02	5	83.33
7	01:02.5	10	68.5
8	01:02.5	5	82.85
9	01:02.5	5	71.4

UV Analysis

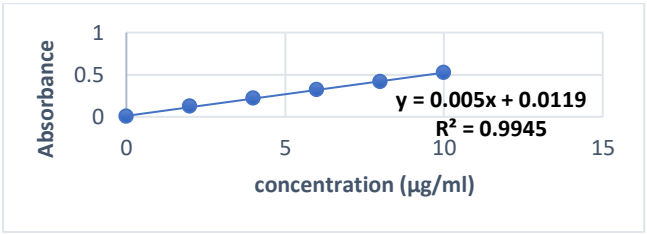

Figure 1: calibration curve of celecoxib

The UV absorption spectrum showed λ max 255nm when scanned range of 400nm -200nm. The drug followed beer's and lamberts law in the range of 0 to 10 µg/ml.

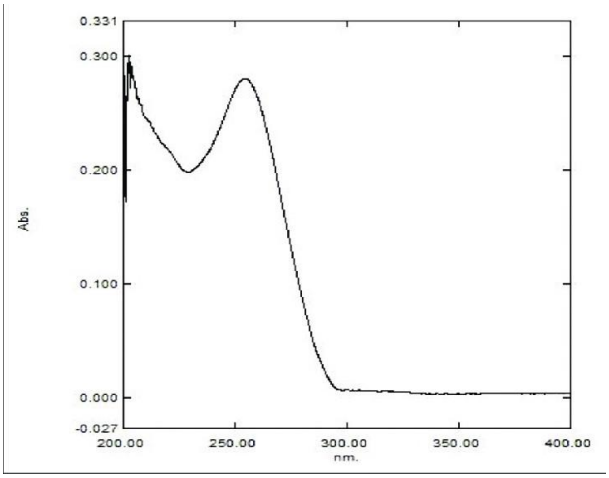

Figure 2: ultraviolet spectra of celecoxib in phosphate buffer

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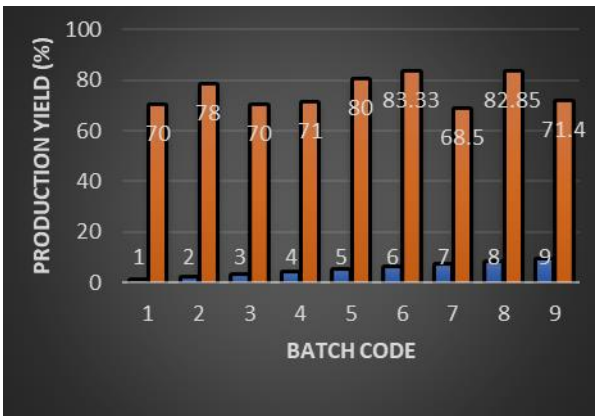
The production yield of all batches of microsponges ranged from 68.50% to 83.33% (Table 3). The drug: polymer ratio was found to affect production yield significantly. For drug: polymer ratio 1:2.5 (F7), production yield was very low i.e. 68.5 % while for drug: polymer ratio 1:2 (F6), it was 83.33%.



Actual Drug Content and Loading Efficiency

The mean amount of drug entrapped in fabricated microsponges was found to be lesser than theoretical value for every drug: polymer ratio employed, in view of the fact that drug encapsulation efficiency did not attain 100%. This was for the reason that some drug gets dissolved in aqueous phase or solvent used.

Table 4: actual drug content and loading efficiency

Batch	Actual drug content (%)	Loading efficiency (%)
1	76	49.2
2	77	68
3	75	75
4	80	62
5	75	67.5
6	86	80
7	78.9	75
8	84.6	78.7
9	78.9	77.4

FTIR

The characteristic peaks of pure celecoxib and formulation are shown in Fig. 4 and Fig. 5 From the data, it was observed that characteristic peaks of drug appeared almost similar in formulation spectrum with disappearance of some peaks. Hence, it can be inferred that there is no chemical interaction between drug and polymer and it can be concluded that the characteristic bands of pure drug were not affected by polymer and method used for preparation.

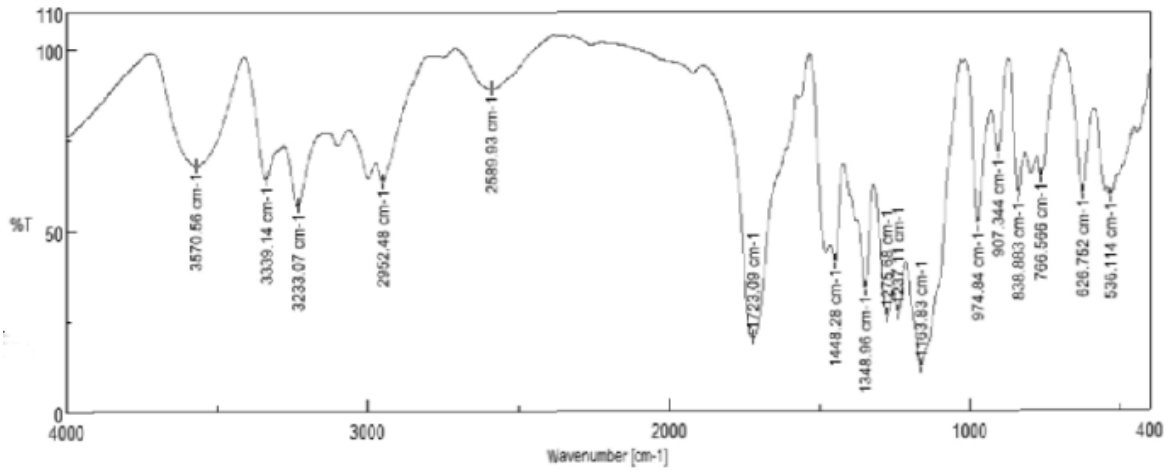


FIGURE 3: FTIR OF DRUG

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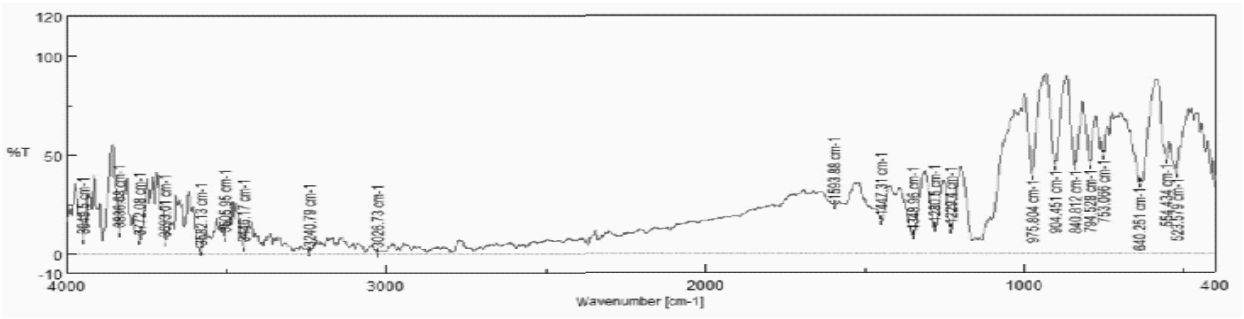


Figure 4:FTIR of microsponges

Scanning Electron Microscopy Analysis

SEM analyses were observed that the microsponges were small, spherical and porous in nature. SEM celecoxib microsponges was shown in figure. Pores were induced by the diffusion of the solvent from the surface of the particles. The appearance of the particles was such that they were termed as the microsponges. For morphology and surface topography investigation, prepared microsponges were subjected to SEM analysis. The captured SEM image of microsponges is shown in Fig. 6

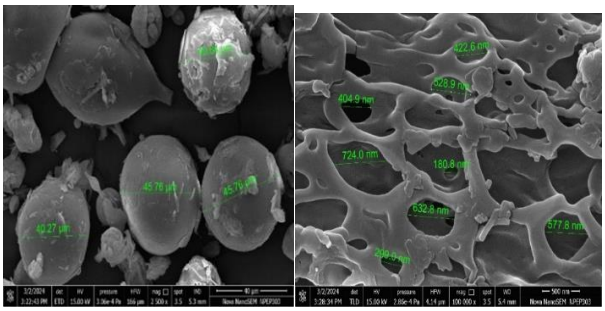


Figure 6: SEM (PORE DIAMETER)

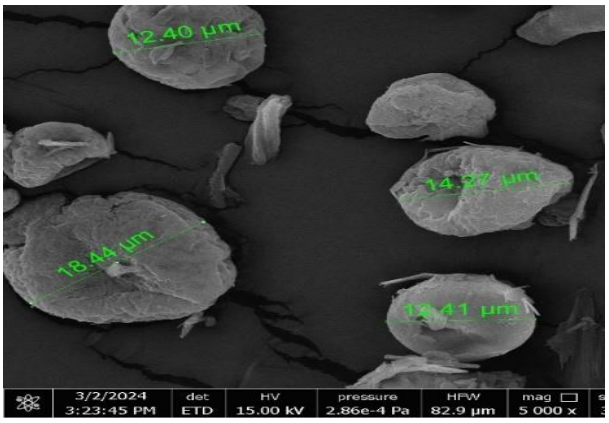
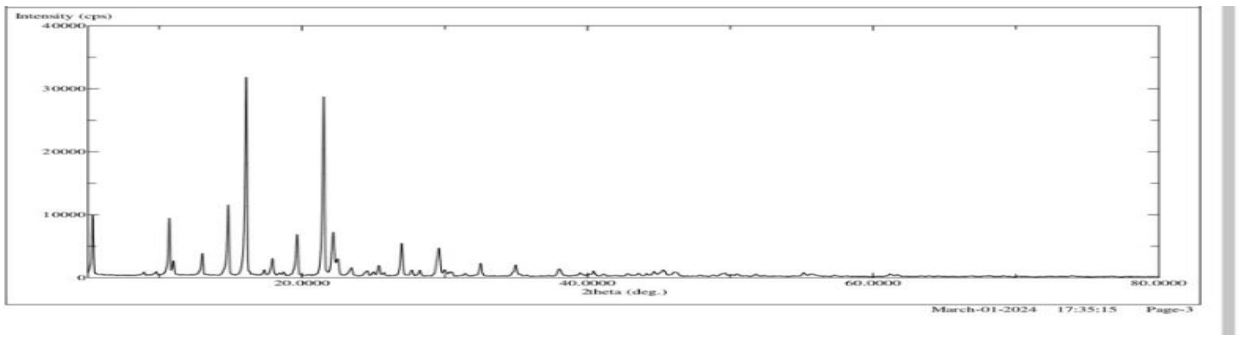


FIGURE 7: SEM

X-ray diffraction study

X-ray powder diffraction (XRPD) method was implied to evaluate physicochemical characteristics of prepared microsponges. Sharp peaks at diffraction angle (2Ɵ) were traced in X-ray diffractograms in case of both drug and its microsponge formulation (Fig. 6). For determination of occurrence of crystal habit modifications and polymorphs in drug crystals, XRPD is a valuable technique.



A)

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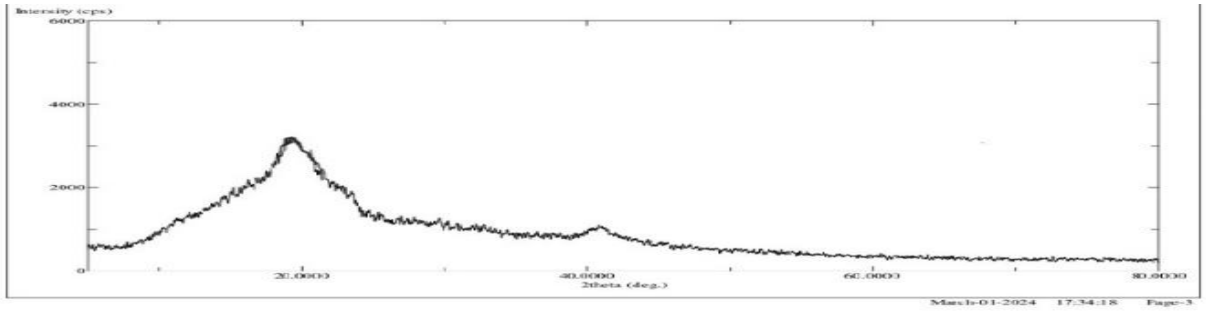

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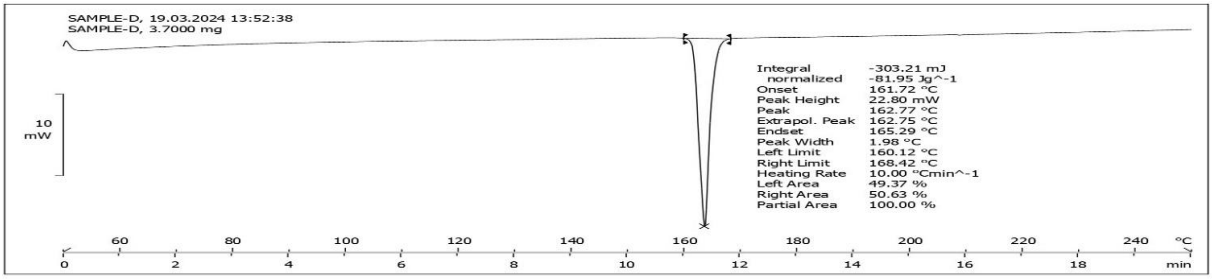
FIGURE 5: A) XRD OF DRUG B) XRD OF MICROSPONGES

DIFFERENTIAL SCANNING CALORIMETRY

A)



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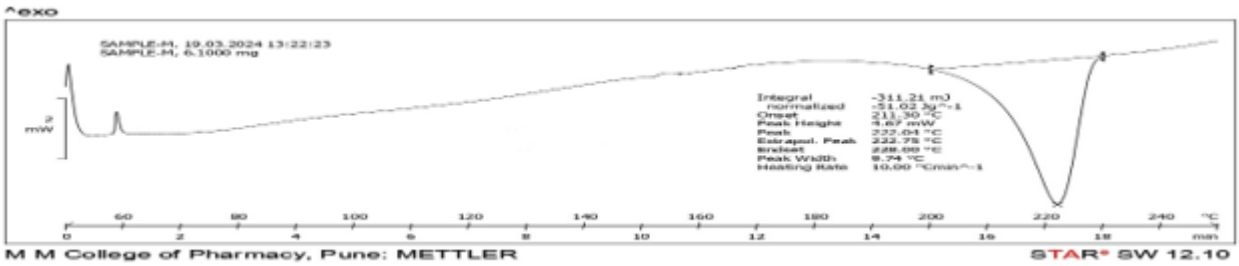

C)

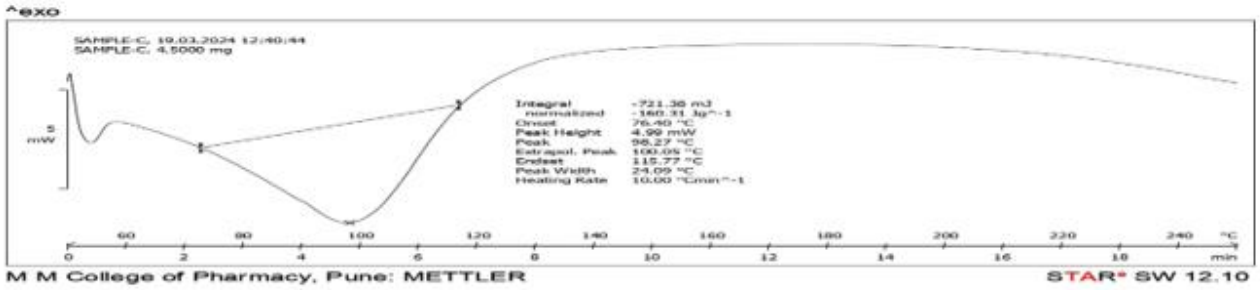

Figure 9: A) DSC of drug B) DSC of microsponges C) DSC of formulation

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Evaluation of celecoxib microsponge cream

Visual inspection

The prepared cream formulations of DDEA microsponges were inspected visually for their color, texture and appearance. All prepared formulations were pearl white, viscous in nature with smooth texZture and of good homogeneity with no any lumps and syneresis.

pH measurement

The pH values of all prepared formulations were found in the range of 6.5–6.8, which are supposed to be suitable to pass up threat of nuisance on application to skin.

Spreadability study

The findings of spreadability depicted that formulated cream get easily spread on applying small amount of shear. The value of spreadability 18.5±0.656 indicated that the cream is easily spreadable by small amount of shear.

Accelerated stability studies:

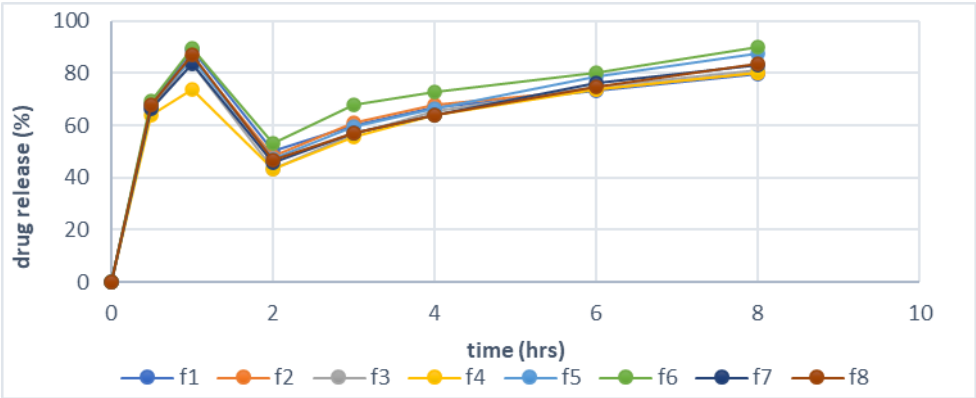
The developed Linalool loaded microsponge formulation was found to be stable upon storage for 3 months. No major changes were noticed in their physical properties and drug release profile

In vitro drug release studies

In vitro drug release studies were carried out for all formulations. Pure drug has shown drug release for 8 h and after that no release was noticed, whereas formulation has shown release till 24 h. In case of formulation, drug release occurred in prolonged manner. In the beginning, drug which is not encapsulated in the inclusions got released. This is the reason for increased % drug release during initial hours. Then, after attaining saturation state, drug release from inclusions occurred. However, in case of pure drug, no encapsulation of drug is seen hence release occurred till 8 h and also since celecoxib is poorly water soluble, drug release was also less. Drug release of all formulation was given in below

Table 5: in vitro drug release of cream

Time (hours)	f1	f2	f3	f4	f5	f6	f7	f8
0	0	0	0	0	0	0	0	0
0.5	67.76	66.88	66.22	63.8	67.89	69.3	66.44	67.98
1	89.3	86.24	83.6	73.6	85.8	89.5	83.84	86.9
2	50.2	48.09	43.56	43.56	47.3	53.24	45.56	46.64
3	60.1	61.07	56.76	55.44	59.4	67.804	56.98	56.98
4	66.88	67.76	65.34	64.02	66.66	72.97	63.8	63.8
6	73.48	73.92	74.58	73.92	78.76	80.41	76.34	75.02
8	79.64	80.08	81.4	80.08	87.78	90.2	83.38	83.6



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CONCLUSION

Controlled drug delivery via the polymer based systems has been proposed to be prevailing both in present and in future; as having numerous potential advantages for scientific as well as economic reasons. The thought behind developing polymeric microsponge delivery system was to deliver celecoxib in a continual manner for extensive time period to reduce application frequency, hypersensitive reactions and to improve bioavailability, safety than marketed conventional formulation. The method implemented was quasi-emulsion solvent diffusion; found to be simple, reproducible and rapid. Formed microsponges were spherical shape, have high porosity and good flow. Formulation with 1:2 drug–polymer ratio was found more efficient to give extended drug release (90.2% at 8 h)

Thus, cream containing microsponges prepared in this study was found to be promising as new-fangled delivery system offering prolonged release of celecoxib to overcome the symptoms of arthritis.

ACKNOWLEDGEMENTS

The authors are thankful to management of Dr. D. Y. Patil college of pharmacy, Akurdi, Pune, for their under support for this project. Our sincere thanks to principal, head of department, and guide for providing necessary support to carry out this research work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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