

Formulation Development and Evaluation of Drug Loaded Microsponges of Sulindac Sodium

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Submission Date: 20-05-2022; Revision Date: 19-06-2022; Accepted Date: 15-07-2022.

ABSTRACT

This research work aimed to develop and evaluate the microsphere formulations for Sulindac sodium. Sulindac sodium a poorly water-soluble drug with high first-pass metabolism is available only as conventional tablets. Thus, an attempt was made to formulate a drug-loaded microsphere to eliminate the first-pass metabolism and also improve the bio-availability of the drug. This work aimed to prepare a stable microsphere formulation of sulindac sodium for the enhancement of bioavailability and reducing the dose frequency. The quasi emulsion solvent diffusion approach was used to create the microspheres. The percentage yield, drug load efficiency, morphological analysis, *in vitro* drug release and stability studies were evaluated. Based on the result selected for the optimized formulation SM5, the morphology of the optimized formulation was by scanned electron microscopy which was found to be uniform and containing pores without any crystals. The formulation SM5 was found to be in an optimized formulation which shows 92.05% release at 12 hr. Stability studies showed that indicated negligible levels of changes were observed in load efficiency, morphological analysis and *in vitro* release, indicating the susceptibility to stability problems during storage at room temperature and 40 °C/75%RH was observed after 3 months. On the basis of the findings, drug-loaded microspheres show improvised release behaviour and provide an effective modified route of administration.

Keywords: Microsphere, Solubility, Porous polymeric system, Sulindac sodium, morphological analysis and *in vitro* drug release.

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INTRODUCTION

Oral administration of medicines is the most common and convenient method of medication administration, resulting in the highest level of patient compliance. The core of pharmaceutical research is the development of orally effective new medications and technology. Oral administration is considerably more successful for medications with high solubility and gastrointestinal permeability, and the creation of pharmaceuticals

with low aqueous solubility or high difficulty is much more difficult.^[1] Even before a medicine reaches systemic circulation, its first-pass metabolism in the GI tract and liver may result in lower bioavailability. To boost the effectiveness of active substances while improving product safety, a novel approach is needed, and microspheres polymeric delivery system might be employed to tackle the challenges.^[2]

The Microsphere polymeric system consists of microscopic sponge-like (porous) spherical particles that may entrap active substances and release them into the systemic circulation over time in response to a trigger. They may also increase the product's visual features and prolong the product's stability due to their unique arrangement.^[3] Microspheres also speed up the solubilization of weakly water-soluble medications

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DOI: 10.5530/ajbls.2022.11.57

by trapping them in the microsponges' small pores. Because these pores are so small, the drug is effectively reduced to microscopic particles, increasing surface area and solubilization rate significantly.^[4]

Sulindac sodium is a nonsteroidal anti-inflammatory medicine (NSAID) that is primarily used to treat rheumatoid arthritis. It is a poorly water-soluble drug with a high first-pass metabolism and is only accessible in the form of traditional tablets. It has anti-inflammatory properties because it inhibits both COX-1 and COX-2, which inhibits prostaglandin formation.^[5]

This work aimed to prepare a stable microsphere formulation of sulindac sodium for the enhancement of bioavailability and reduced dose frequency.

MATERIALS AND METHODS

The following materials available were supplied by the manufacturer, Sulindac Sodium (Tokyo Chemical Industry), Eudragit and Triethyl Citrate (a free gift sample from KMS Health Centre, Chennai), Polyvinyl Alcohol, Ethanol

Preparation of microsponges^[6-8]

Porous microsponges were also made using a quasi-emulsion solvent diffusion process utilising an interior phase containing a polymer such as Eudragit dissolved in ethanol. The medication is then progressively added to the polymeric solution and dissolved at 35°C using ultrasonication, with a plasticiser such triethyl citrate (TEC) added to increase plasticity. As a result, the inner phase is transferred to the external phase, which comprises polyvinyl alcohol and distilled water, and constantly agitated for 1 hr. After that, the microsponges were isolated from the mixture by filtering it. In an air-heated oven at 40°C, the product was cleaned and dried for 12 hr. The preparation procedure is shown in the Table 1.

Evaluation Studies of Microsponges

Preformulation studies

UV-VIS spectrophotometer evaluation^[9]

A Shimadzu spectrophotometer was used to gather ultraviolet and visible spectra (UV-Vis) in the 200–800 nm range, and a 2.5 X 10⁻⁵ mol L⁻¹ ethanolic solution was created for this research.

Standard Calibration Graph of Sulindac sodium^[10]

In a volumetric flask (100 ml), a weighed quantity of medication (100 mg) was dissolved in a little amount of ethanol. Finally, ethanol (Stock I, 1000mg/ml) was used to get the volume up to the required level. Stock II was

Ingredients	SM1	SM2	SM3	SM4	SM5
Inner phase					
Sulindac sodium (mg)	100	100	100	100	100
Eudragit (mg)	100	80	60	40	20
Ethanol (ml)	10	10	10	10	10
Outer phase					
PVA (mg)	50	50	50	50	50
Water (ml)	200	200	200	200	200

Sl/no	Concentration	Absorbance
1.	0	0.0000
2.	1	0.1525
3.	2	0.2268
4.	3	0.3362
5.	4	0.4216
6.	5	0.5037
7.	6	0.5922
8.	7	0.7297
9.	8	0.7815
10.	9	0.8395
11.	10	0.8917

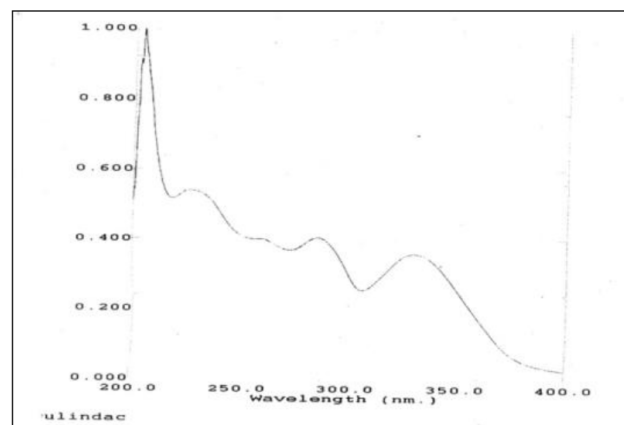


Figure 1: UV spectrum of pure drug.

created by mixing 10ml of main stock with 100ml of volumetric flask and adjusting the volume to the mark (Stock II 100g/ml). Stock III was created by mixing 10ml of main stock with 100ml of volumetric flask and adjusting the volume to the mark (Stock III 10g/ml). Different concentrations of solutions (i.e. 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10g/ml for ethanol) were produced from the aforesaid stock solutions and analysed using a UV-visible spectrophotometer at 202 nm. The preparation procedure is shown in Table 2 and Figures 1-2.

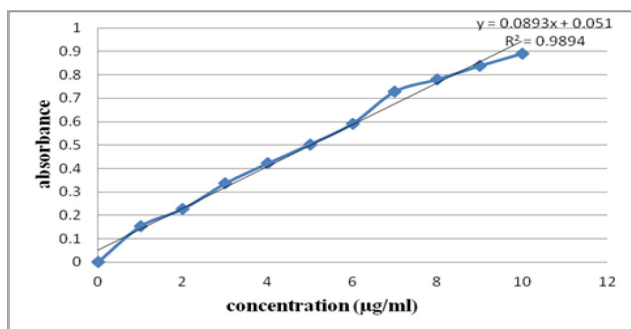


Figure 2: Calibration curves of pure drug.

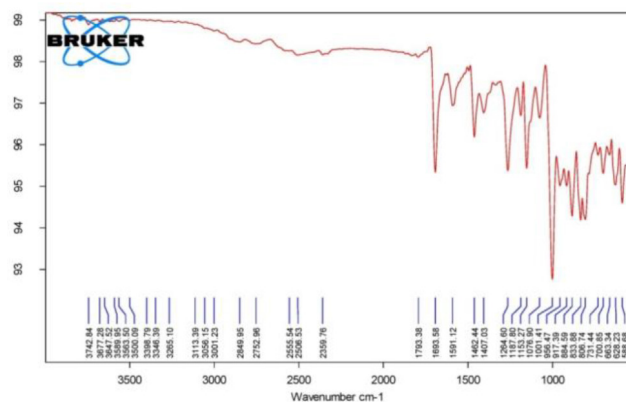


Figure 3: IR spectrum of Sulindac sodium.

Compatibility studies^[11]

The IR spectrum of pure drug, a physical combination of drug and excipients, and formed microspunge were taken in an ATR-FTIR spectrometry sample holder and studied for any presence in compatibility produce. The preparation procedure is shown in the Figure 3-4.

Production yield^[12]

It is calculated to determine the efficacy of any methodology, assisting in the selection of the best production method. The Practical yield was calculated by dividing the number of microsponges recovered from each preparation by the total amount of starting material after the formulations were prepared (Theoretical yield). The formula below may be used to compute it. The preparation procedure is shown in the Table 3.

$$\text{Pr oduction yield} = \frac{\text{Practical yield}}{\text{Theoretical yield (drug + polymer)}} \times 100$$

Drug load efficiency^[13]

100 mg of the prepared microscope were dissolved in ethanol in an a100ml volumetric flask and made up to the mark after the proper dilution absorbance of the drug was measured with a UV spectrometer at 202 nm.

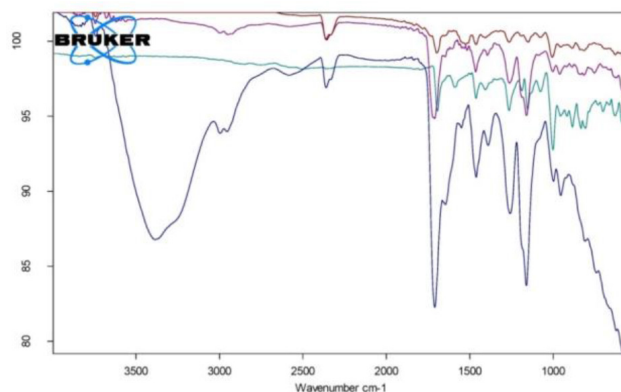


Figure 4: IR spectrum of physical mixtures of drug and excipients.

Determination Percentage yield and Drug load efficiency

Table 3: Percentage yield and Drug load efficiency.

Formulation code	Percentage yield	Drug load efficiency
SM1	77.84	75.5
SM2	81.11	77.9
SM3	84.43	80.3
SM4	87.85	83.8
SM5	91.66	85.6

the following calculation can be used to calculate the load efficiency of the drug. The preparation procedure is shown in the Table 3.

$$\text{load efficiency} = \frac{\text{the actual drug content in microspunge}}{\text{theoretical drug content}} \times \text{heo}$$

Morphology determination by scanning electron microscopy (SEM)^[14]

The Morphology of the prepared microsponges was determined using scanning electron microscopy. The SEM may be used to characterize the shape and size of microscopic objects in relation to particle size. An electron beam was used to scan the material in a regulated pattern in an evacuated chamber. The SEM images of optimized drug-loaded microspunge formulation (SM5) and pure drug were scanned at various magnifications of 250X, 20.00 K X, and 30.00 K X. The preparation procedure is shown in Figure 5.

In vitro drug release^[15-16]

In vitro experiments were performed by dialysis method with a compartment capacity of 900 mL and a cellophane membrane. The prepared microspunge was kept across the membrane, and the diffusion cell's compartment

SEM Analysis

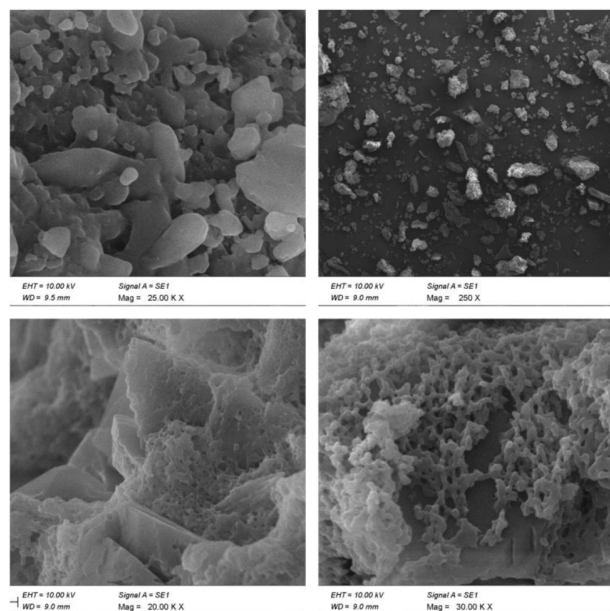


Figure 5: SEM analysis of prepared microsp sponge.

Table 4: *In vitro* drug release of microsp sponge.

Formulation Code	SM1	SM2	SM3	SM4	SM5
Time in hrs	% Cumulative Drug Release				
0	0	0	0	0	0
0.5	11.43	15.94	19.51	21.74	24.84
1	19.85	23.18	28.13	35.06	37.96
3	27.06	29.98	33.63	47.38	49.95
5	34.59	38.82	46.06	52.82	62.50
7	48.79	51.14	55.03	61.10	76.29
9	55.97	62.69	68.98	75.84	84.62
12	62.10	66.46	74.37	81.22	92.05

was filled with pH 5.5 acetate. The whole thing was held together by a magnetic stirrer. The solution in the receptor compartment was continually swirled at 50 rpm with a magnetic bead, and the temperature was maintained at 32°C. The samples were taken at various intervals up to 12 hr and examined for a percentage of drug release from the microsp sponge by using a UV spectrophotometer at 202nm. The preparation procedure is shown in the Table 4 and Figure 6.

Determination of short-time stability studies for microsponges^[17-18]

The optimized formulation of microsp sponge for the stability determination accelerated stability conditions at (40°C/75%RH). It's taken and examined for load efficiency and *in-vitro* drug release studied every 30 days

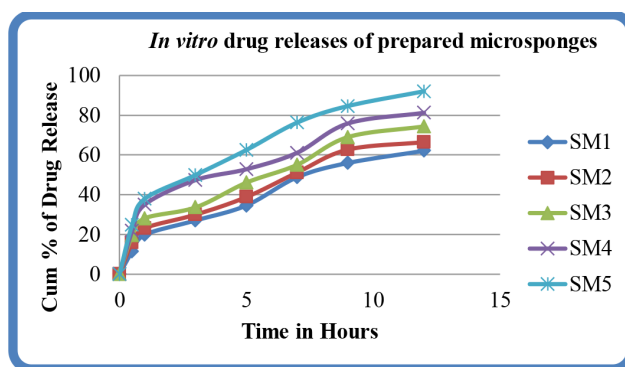


Figure 6: Graph of *in-vitro* Drug Release.

Stability Study for the Optimized SM5 Formulation

Table 5: Stability Parameter of the optimized formulation.

Parameters	Initial	After one month 40/75 (°C/ RH)	After the second month 40/75 (°C/ RH)	After the third month 40/75 (°C/ RH)
Load efficiency%	85.6	85.2	84.7	83.9
<i>In vitro</i> drug release	92.05	91.67	90.85	90.15

for a period of 3 months. All of these factors are compared to the initial sample and evaluated to see whether it meets the specifications. If it does, the batch passes the test. The preparation procedure is shown in the Table 5.

RESULTS AND DISCUSSION

Pre-formulation studies^[19]

UV-VIS spectrophotometer evaluation

UV spectrophotometric analysis the maximum absorbance of the drug was found to be 202nm and good linearity with R² value of 0.989, which suggests that it obeys the Beer-Lamberts law.

Compatibility studies by ATR-FTIR

The complete principal drug peaks were seen at 1793.38 (C=O stretching), 1693.58 (C-C stretching), 1462.44 (C-H stretching), 14075 (S=O stretching), 1187.90, 1264.60 (C-F stretching) during ATR-FTIR tests to determine the physicochemical interaction between drug and excipients employed in microsp sponge. Sulindac peaks were identified in the spectra of the SM5 formulation. These findings revealed that no chemical interactions occurred throughout the microsp sponge production process.

SEM Analysis

SEM analysis was studied for the optimized drug-loaded microsphere formulation (SM5) and the pure drug was evaluated for the surface morphology of the formulations at magnifications of 250X, 20.00 K X, and 30.00 K X. These images revealed that the prepared microsphere was finely spherical and homogenous, with no detectable drug material.

Determination Percentage yield and Drug load efficiency^[20]

The percentage yield, Load efficiency of sulindac microsphere showed percentage yield ranging from 77.84 to 91.66% and drug load efficiency 75.5 to 85.6 mg respectively, From the result, increasing drug-polymer concentration increase the percentage yield and load efficiency of microsphere.

In vitro Drug Release^[21]

From the above result, the *in vitro* release studies of gel from an optimized formulation of SM5 microsphere were performed on the formulations SMG1 to SMG4. 91.22% of drug release from SMG4 formulation was observed after a time period of 12 hrs and compared with the release of pure drug. In comparison, SMG4 formulation exhibited reasonably, easily spreadable and good texture with the release of the drug, hence it was considered the optimized formulation.

Stability Study for the Optimized SM5 Formulation

The improved formulation was subjected to a 3-month stability assessment at 40°C/75 % RH, as per ICH guidelines. The findings revealed that there was no significant change in the physical and chemical parameters of the microsphere at the end of the third month, indicating that the formulation (SM5) was stable.

SUMMARY AND CONCLUSION

Based on the results of the studies, it is concluded that the Sulindac-loaded microsphere formulation especially SM5 microsphere formulation exhibited improvised release behaviour, which would help in minimizing the dose frequency, improve the patient compliance and provide an effective modified route of administration.

ACKNOWLEDGEMENT

The authors are thankful to Dr. B.Jaykar, Professor and Registrar, Vinayaka Mission's Research Foundation (Deemed to be University) and Vinayaka Mission's College of Pharmacy, Salem, Tamil Nadu for extending their support and facilities for this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ATR-FTIR: Attenuated Total Reflectance- Fourier Transform Infrared; **COX:** Cyclo Oxygenase; **Nm:** Nanometer; **PVA:** Poly Vinyl Alcohol; **SM1:** Sulindac Microsphere 1.

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Cite this article: Pethappachetty P, Chandira RM, Kumaresan K, Samy DA. Formulation Development and Evaluation of Drug Loaded Microsponges of Sulindac Sodium. *Asian J Biol Life Sci.* 2022;11(2):423-8.