International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 6, 2024

Original Article

DEVELOPMENT, OPTIMIZATION AND ASSESSMENT OF NAPROXEN MICROSPONGES BY BOX-BEHNKEN DESIGN AS A TARGETTED AND CONTROLLED RELEASE DRUG DELIVERY

SONIA GUPTA*, JYOTI GUPTA

IEC School of Pharmacy, IEC University, Baddi, Himachal Pradesh, India
***Corresponding author: Sonia Gupta; *Email: singla.sonia28@gmail.com**

Received: 12 Jun 2024, Revised and Accepted: 18 Aug 2024

ABSTRACT

Objective: Due to weak physical, chemical stability and poor bioavailability of Naproxen conventional dosage form; the purpose of this work is to improve formulation stability, additionally to accomplish highest possible concentration of the drug in the blood by preparing Naproxen loaded microsponges.

Methods: Naproxen Microsponge (NM) was created utilising the quasi emulsion technique. In this process Ethyl Cellulose (EC) acts as a polymer, Poly Vinyl Alcohol (PVA) acts as the emulsifier, and Dichloromethane acts as the solvent. To investigate how changes in different formulation and processing parameters affect important product qualities, a Box Behnken Design (BBD) was used. Particle Size, Percentage Yield, and Entrapment Efficiency (%EE) were selected as response factors, whereas independent variables including EC quantity (X1), PVA concentration (X2), and Stirring Speed (X3) were selected as independent variables.

Results: The microsponges underwent thorough analysis using Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FT-IR), X-Ray Diffraction (XRD), and Particle Size analysis. The evaluation included studying the morphology, drug loading, and *in vitro* drug release. The compatibility studies showed no chemical interactions between the drug and the polymers used. It was observed that the ratio of drug to polymer had a significant impact on drug content, EE and particle size. The SEM results revealed that the microsponges were spherical with a porous surface and had a mean particle size of 15.15 µm. The *in vitro* drug release studies demonstrated that the optimized Naproxen Microsponge Formulation (NMF2) achieved over 80% extended drug release by the end of 8 h, following the Corsmeyer Peppas Model.

Conclusion: The Naproxen loaded microspheres possessed a sustained release with improved bioavailability and better stability.

Keywords: Naproxen microsponges, Ethyl cellulose, Quasi emulsion technique, Box behnken design, *In vitro* drug release, Kinetic study

DOI: https://dx.doi.org/10.22159/ijap.2024v16i6.51765 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The current project aims to develop Microsponges that contain naproxen and limit the release of the drug into the skin. Microsponges are small, strong spheres made of polymeric materials, ranging in size from 5µm to 300 µm [1]. These spheres slowly release various active compounds, making them stable, non-toxic, non-allergenic, non-mutagenic, and highly effective [2]. The Microsponge-based Delivery Systems (MDS) ensure that medication is applied to the skin's surface and within the epidermis, reducing both systemic and local skin-related issues [3]. They provide controlled drug release and are safe for biological systems. Additionally, this technique offers several benefits, such as improved flexibility, fewer side effects, more elegant formulations, and increased stability [4]. Naproxen is a synthetic, moderately potent Non-Steroidal Anti-Inflammatory Drug (NSAID) used to treat musculoskeletal disorders, arthritis, and provide pain and inflammation relief. It belongs to Biopharmaceutics Classification System (BCS) class II, characterized by low solubility and high permeability [5]. Its chemical name is propanoic acid (2-(6-methoxynaphthalen-2-yl)). Naproxen is a white crystalline powder that is insoluble in water but easily soluble in ethanol, methanol, and dichloromethane. Its mechanism of action involves the inhibition of the enzyme Cyclooxygenase (COX-1 and-2), which is responsible for generating prostaglandin from Arachidonic acid [6, 7]. The therapeutic effects of Naproxen can last up to 7-8 h following oral treatment. Topical medication distribution is a successful therapeutic approach for treating localized dermatologic conditions due to its superior absorption and ability to penetrate the skin more deeply [8]. The use of percutaneous absorption enhancers or suitable carriers is necessary to improve therapeutic efficacy following topical medication administration. Efforts have been made to enhance the transdermal penetration of naproxen gel [9]. The current study aims to formulate, optimize, and evaluate various microsponge formulations. The quasi-emulsion solvent diffusion method is used to manufacture microsponges from Ethyl Cellulose (EC) and Poly Vinyl Alcohol (PVA) solutions [10]. Optimization is achieved through the Box Behnken Design (BBD). Furthermore, characterization is performed using Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) analysis [11].

MATERIALS AND METHODS

Materials

Life Biomax Biotechnics (P) Ltd, based in Alipur, Barwala Dist, Panchkula (HR), generously provided a complimentary sample of naproxen. Additionally, Central Drug House Pvt. Ltd. was the dedicated supplier of EC and Carbopol 940.

Method for preparation of naproxen microsponges

"Naproxen-loaded microsponges were prepared using the quasi-emulsion solvent diffusion technique. A precise amount of naproxen and EC was dissolved in dichloromethane for the organic phase. Additionally, 1% Di Butyl Phthalate (DBP) acting as a plasticizer, was added to the organic phase. The prepared organic phase, acting as the external phase, was slowly added to the PVA solution while continuously stirring. Complete homogenization led to the evaporation of solvent, resulting in the formation of microsponges. Subsequently, the microsponges were cleaned, filtered, and dried for 12 h at 40 °C [12].

Design of experiment

The main characteristics of micro-sponge were shown to be significantly influenced by the polymer concentration, amount of PVA, and stirring speed during initial trials. An investigation of the degree to which changes in independent variables affect important

product attributes was conducted using the BBD [13]. Particle size, Entrapment Efficiency (%EE) and %yield were chosen as dependent variables, polymer concentration, PVA quantity, and homogenising speed were chosen as independent variables as shown in table 1 and 2 with its coded and transformed values and table 3 contained optimized formulation variables.

Table 1: Coded values in BBD

Coded values		Levels		
		1	**0**	**-1**
X1	EC concentration (mg)	600	400	200
X2	PVA concentration (ml)	50	60	70
X3	Stirring speed (rpm)	1500	1250	1000

Table 2: Composition table of planned batches

Formulation code	Coded value			Transformed value		
	EC concentration (mg) (X1)	**PVA concentration (ml) (X2)**	**Stirring speed (rpm) (X3)**	**EC concentration X1 (mg)**	**PVA concentration X2 (ml)**	**Stirring speed X3 (rpm)**
NM1	1	0	1	600	60	1500
NM2	-1	0	1	200	60	1500
NM3	0	0	0	400	60	1250
NM4	0	0	0	400	60	1250
NM5	0	1	1	400	50	1500
NM6	0	0	0	400	60	1250
NM7	0	-1	-1	400	70	1000
NM8	0	-1	1	400	70	1500
NM9	0	1	-1	400	50	1000
NM10	-1	-1	0	200	70	1250
NM11	1	0	-1	600	60	1000
NM12	-1	0	-1	200	60	1000
NM13	0	0	0	400	60	1250
NM14	1	1	0	600	50	1250
NM15	-1	1	0	200	50	1250
NM16	1	-1	0	600	70	1250
NM17	0	0	0	400	60	1250

NM-Naproxen microsponge

Evaluation parameters of intended batches

Determination of particle size

Particle size analyzer was used to measure the size of the microsponges after they had been suitably diluted with double-distilled water [14].

Percentage practical yield

The ratio of the final weight of the dried microsponges to the total weight of the raw ingredients was used to calculate the % yield. The following formula can be used to calculate the practical % yield [15].

$$\text{Weight of dried microsponges} = \frac{\text{Practicalyield}}{\text{totalmass (drug+plasticizer+polymer)}} \text{X100}$$

Microsponges' drug loading efficiency and entrapment efficiency

After weighing and crushing 50 mg of microsponges, they were mixed with 50 ml of phosphate buffer (pH 6.8). The mixture was then sonicated for thirty minutes to extract as much medicine as possible from the microsponges. The volume was increased to 100 ml using the same solvent and then passed through a filter paper with a pore size of 0.45 µm. The absorbance of this solution was measured at 230 nm using a UV-visible spectrophotometer (PC-based double beam spectrometer 2202), in comparison to a blank phosphate buffer with a pH of 6.8. Formulas from reference [16] were used to calculate the microsponge loading efficiency (%) and %EE.

$$\text{Percentage drug loading efficiency} = \frac{\text{Actual drug content in weighted microsponge}}{\textbf{Microspongeweight}} \text{X } 100$$

$$\text{Percentage entrapment efficiency} = \frac{\text{Actual drug content in weighted microsponge}}{\textbf{Theoretical drug content in weighed microsponge}} \text{X } 100$$

***In vitro* dissolution studies**

Drug-loaded microsponges were placed in the basket containing 500 ml of pH 6.8 phosphate buffer solution and spun at 50 rpm. To maintain the sink condition, five milliliters of dissolving media were withdrawn at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h. An equal amount of newly heated dissolving medium was added immediately. Samples were filtered through 0.45 µm membrane paper and analyzed for drug content using a UV-visible spectrophotometer at 230 nm [17].

Evaluation parameters of optimized naproxen microsponges formulation

Morphology

Microsponges have their morphology which was examined via SEM. A gold/palladium conductive coating was applied to an aluminium stub using double-sided tape. After that, they were detected at 15.00 kV accelerating excitation voltage [18].

Particle size evaluation

The mean Particle Size of Naproxen-loaded microsponges was determined using an optical binocular microscope equipped with a calibrated eye piece. A minimum quantity of microsponge was put to a cleaned slide, and the quantity of particles in each batch was counted [19].

Drug-polymer compatibility

KBr pellets were utilized to perform FTIR spectroscopy compatibility studies between the drug and polymer in the 4000–400 cm−1 range.

Differential scanning colorimery study

Comprehending the polymorphism properties of a medication in its formulation is essential for determining its rate of dissolution,

bioavailability, and effectiveness as a treatment. Therefore, it was essential to investigate the drug's polymorphism in the microsponges. Standard aluminium pans were used to contain optimized microsponges and pure medication (5 mg). These samples were scanned from 20 to 350 °C at a rate of 5 °C per minute. As a point of reference, sealed empty pans were also utilized [20].

X-ray differaction study

Using a crystal monochromator and a Cu K-α1 radiation with a wavelength of 1.5405A°, an X-ray diffractometer (Siemens, Model D5000, Germany) was used to capture the diffraction patterns. The device was running at 20 A° of current and 45 mV of voltage. "In order to" characterize the crystal and physical state of naproxen and its microsponges, diffraction patterns were run at a rate of 5–10 °C/min for two hours [21].

RESULTS AND DISCUSSION

Physical appearance

Using a quasi-emulsion solvent diffusion approach, microsponge particles with a fairly white tincture were produced; these particles had better flow characteristics than pure medication.

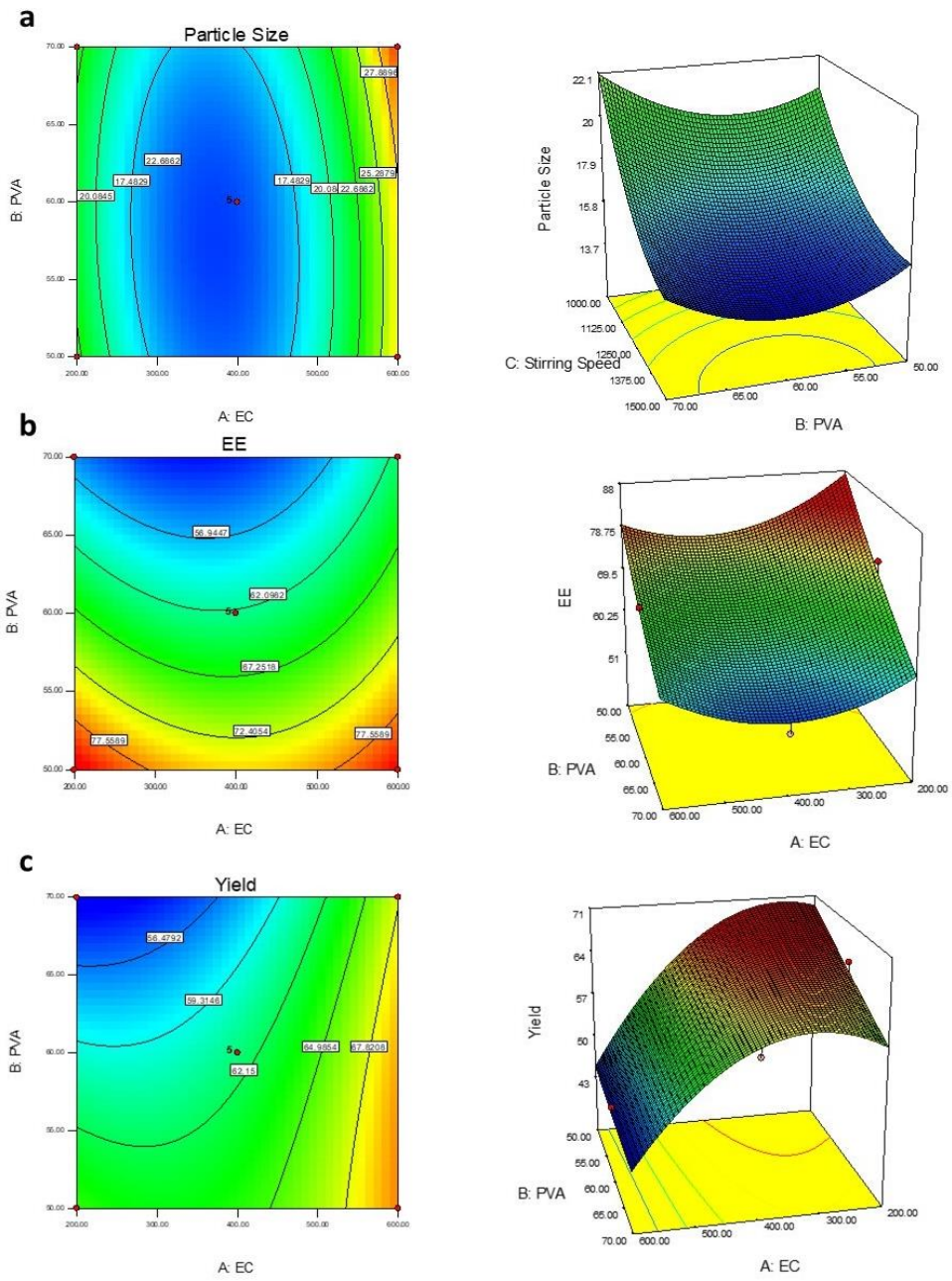

Fig. 1: Contour plot and 3D response surface plots for a. Particle size, b. %EE c. % yield

Response surface analysis of models for particle size, % EE and % yield

Particle size

The size of the microsponges was significantly influenced by the drug/polymer ratio and stirring speed, as demonstrated by the regression analysis results. Specifically, it was demonstrated that the size of the microsponges decreased with increasing homogenization speed, indicating a negative linear connection between homogenization speed and microsponge size. The intense mechanical shear force produced at faster stirring rates, which promotes the quick dispersion of organic phase globules and prevented smaller, scattered

globules from aggregating into larger droplets. This result is consistent that showed that as homogenization speed increased, microsponge size decreased [22] as shown in fig. 1.

Entrapment efficiency study

The designed batches' %EE ranged from 51.2 to 82.1%. With an efficiency of 82.1%, the NM 11 batch was the most efficient, while NM 6 had the lowest efficiency at 51.2%. The amount of PVA and polymer concentration, out of all the independent variables, significantly impacted the drug EE (fig. 1). Polymer concentration had a favourable impact on microsponges' EE, PVA concentration had a negative influence. The enhanced presence of PVA in the outer phase resulted in improved drug solubility in water, perhaps facilitating more drug transfer from the microsponges to the aqueous phase and diminishing the microsponges' capacity to trap particles [23].

Percentage yield

Across the planned batches, the percentage product yield ranged from 54.2% to 70.8%. All independent factors had a substantial impact on the % yield, as demonstrated by the regression analysis. Significantly, the yield was most affected by polymer concentration, then by homogenization speed and PVA content. Through an increase in viscosity, the enhanced polymer concentration most likely slowed the pace at which the internal organic phase diffused into the external aqueous phase. Because of the slower diffusion, droplet formation and polymer solidification had more time to occur, increasing the % yield.

Table 3: Comparative result data of all microsponges formulation

Code	Size (µm)	% EE	% Yield	Drug release in 0.25 h	Drug release in 8 h
NM1	27.45± 1.3	69.4± 1.2	70.8± 1.6	25.54±1.574	87.3±3.64
NM2	20.1± 2.3	75± 1.6	65±1.3	27±1.59	94.41±1.176
NM3	14.21±3.4	60.12±2.1	61.21± 1.7	20.43±1.975	83.5±1.472
NM4	17± 2.1	75.2±1.8	64.7± 2.1	22.41±3.468	85.2±1.807
NM5	20.1± 4.5	57.2±2.0	59.85± 1.9	28.57±1.457	93.71±2.157
NM6	14.2±2.4	51.2± 1.5	58.1± 2.4	24.1±1.698	87.96±2.286
NM7	21.5±1.1	81.6± 1.9	66.5± 2.6	22.78±1.99	91.78±3.184
NM8	25.3±1.6	55.2± 2.2	54.2± 1.8	25.56±1.505	87.06±3.462
NM9	31.44± 1.8	75.8± 2.4	73.3± 1.6	24.97±1.978	92.29±1.229
NM10	26.5± 1.5	67.3±1.6	56.1± 2.2	25.86±1.298	93.61±1.348
NM11	25.38±2.1	82.1±2.4	70.1± 2.5	28.91±2.345	91.88±1.843
NM12	21.5±2.3	81.2± 3.2	65.3± 3.3	32.19±1.494	93.21±1.065
NM13	32.14± 2.5	64.5± 3.5	66.8± 3.6	27.65±1.363	94.74±1.277

Results are expressed as mean±SD, n=3, %EE-Entrapment Efficiency, %yield-Yield in percentage

Designed batch *in vitro* drug release study

Fig. 1 shows design batch *in vitro* drug release analysis findings. Every design batch showed a burst release because of the microsponges' porosity and the drug particles that were present on their surface [25]. Of these lots, NM8 had the least amount of burst release, and NM6 had the most. In less than an hour, more than 40% of the medicine was released from each design batch, and in six hours, more than 80%. To ensure regulated medication release at the application site, microsponges were prepared. A prolonged pharmacological impact could be harmed by excessive release in a brief amount of time, whereas an excessively sluggish release could prevent the drug from reaching the minimal therapeutic concentration. To ensure a prompt attainment and sustained maintenance of the minimum effective concentration, the following criteria for drug release were established in this study: between 25% and 40% at 0.25 h and more than 80% at 6 h as shown in fig. 2 and 3.

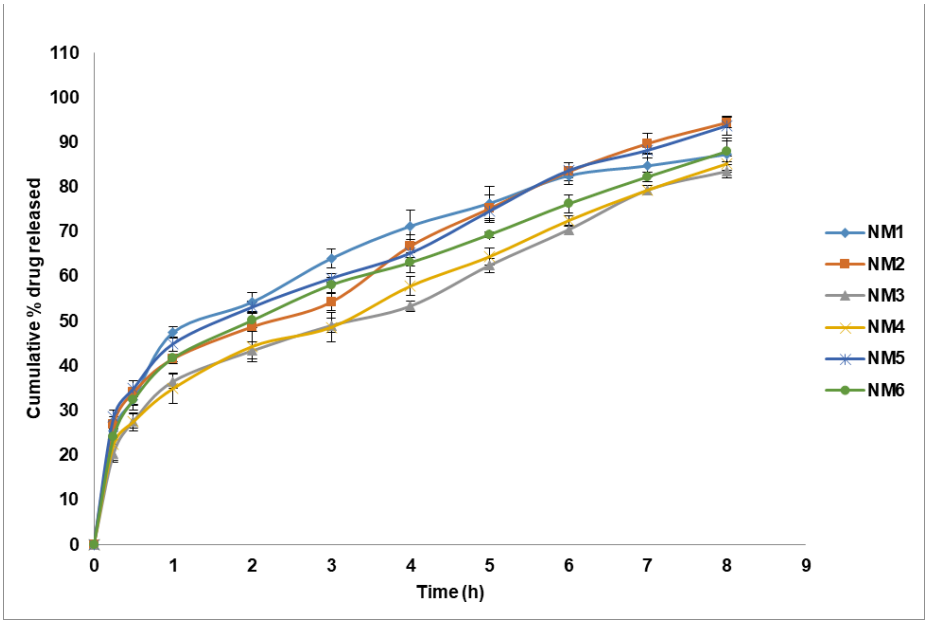

Fig. 2: Graph of *in vitro* drug release study of formulation NM1-NM6, Error bar indicates SD of n=3

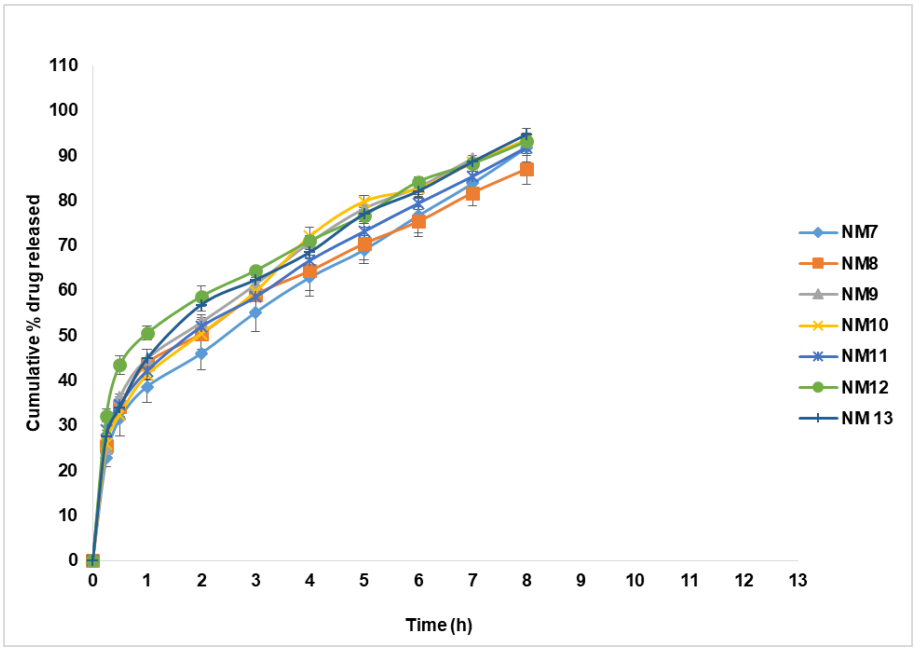

Fig. 3: Graph of *in vitro* drug release study of formulation NM7-NM13, Error bar indicates SD of n=3

Release kinetic of all formulation

The drug release process was examined using various equations, including First order, Zero order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell and values of various parameters were calculated as shown in table 5 and 6.

Analysis of validation batches

Optimized Naproxen Microsponge Formulations (NMF1 and NMF2) was designed and evaluated various responses as shown in table 7 and 8. Actual responses of these two formulations were compared with predicted response of BBD.

Table 5: Release kinetic of formulation NM1 – NM7

Model	Parameters	NM1	NM2	NM3	NM4	NM5	NM6	NM7
Zero Order	R^2	0.83373	0.9699	0.9774	0.9787	0.9572	0.9582	0.977
	Slope	8.990	8.692	7.6675	7.8772	8.4077	7.9315	8.3272
	Intercept	26.86	12.464	9.4868	9.6905	14.926	13.56	10.937
First Order	R^2	0.9767	0.9224	0.9565	0.9606	0.9375	0.9734	0.9267
	Slope	-0.1034	-0.1127	-0.0724	0.0759	-0.1067	-0.0834	-0.0936
	Intercept		2.083	2.0228	2.027	2.0531	2.013	2.0542
Higuchi	R^2	0.97023	0.9736	0.9706	0.9706	0.9874	0.9919	0.9774
Model	Slope	29.41	30.265	26.555	27.09	29.678	28.045	28.947
	Intercept	10.08	-5.8947	-6.4167	-6.5076	-3.6561	-4.0671	-6.554
Hixon	R^2	0.83373	0.9699	0.9774	0.9787	0.9572	0.9582	0.977
Crowell	Slope	-2.997	-2.8973	-2.558	-2.6091	-2.8026	-2.6438	-2.7757
	Intercept	24.378	29.179	30.171	30.103	28.358	28.813	29.688
Corsme yer	R^2	0.98886	0.9627	0.9921	0.9681	0.9798	0.9938	0.9887
Peppas	Slope	0.3639	0.5203	0.5709	0.558	0.4995	0.5579	0.5762
	Intercept	1.6348	1.3971	1.293	1.3103	1.4271	1.3646	1.3361

Table 6: Release kinetic of formulation NM8 – NM13

Model	Parameters	NM 8	NM 9	NM10	NM 11	NM 12	NM 13
Zero order	R^2	0.9459	0.9615	0.8927	0.9551	0.9151	0.9325
	Slope	7.7332	8.7979	6.2106	8.1482	7.9755	8.5262
	Intercept	15.153	12.952	15.863	14.958	20.369	15.273
First order	R^2	0.9809	0.9602	0.926	0.9504	0.9633	0.9357
	Slope	-0.0806	-0.1104	-0.0512	-0.0957	-0.1032	-0.111
	Intercept	1.9969	2.0637	1.9484	2.0304	2.0048	2.0357
Higuchi model	R^2	0.9961	0.9804	0.977	0.9888	0.9981	0.9961
	Slope	27.58	30.876	22.58	28.813	28.949	30.234
	Intercept	-2.5155	-6.1249	0.7943	-3.1547	1.1158	-3.4851
Hixon crowell	R^2	0.9459	0.9615	0.8927	0.9551	0.9151	0.9525
	Slope	-2.5777	-2.9326	-2.0702	-2.7161	-2.658	-2.8421
	Intercept	28.282	29.016	28.046	28.347	26.544	28.422
Corsmeyer peppas	R^2	0.9948	0.9645	0.9862	0.9665	0.9978	0.9778
	Slope	0.5307	0.5953	0.4364	0.4942	0.4436	0.5473
	Intercept	1.3927	1.3677	1.3954	1.4238	1.503	1.4103

Table 7: Validation of batches NMF1 and NMF2: predicted response

S. No.	EC	PVA	Steering speed	Particle size	EE (%)	% yield
1	266.13	50	1500	17.594926	82.0999	67.41499
2	261.01	50	1500	17.8575	82.444	67.5248

Table 8: Validation batches NMF1 and NMF2: actual response

S. No.	EC	PVA	Stirring speed	Particle size	EE (%)	% yield
1	266.13	50	1500	19.32	79.23	66.53
2	261.01	50	1500	15.15	83.31	68.21

NMF-Optimized Naproxen Microsponge Formulations, EE= Entrapment Efficiency, EC= Ethyl Cellulose, PVA=Poly Vinyl Alcohol.

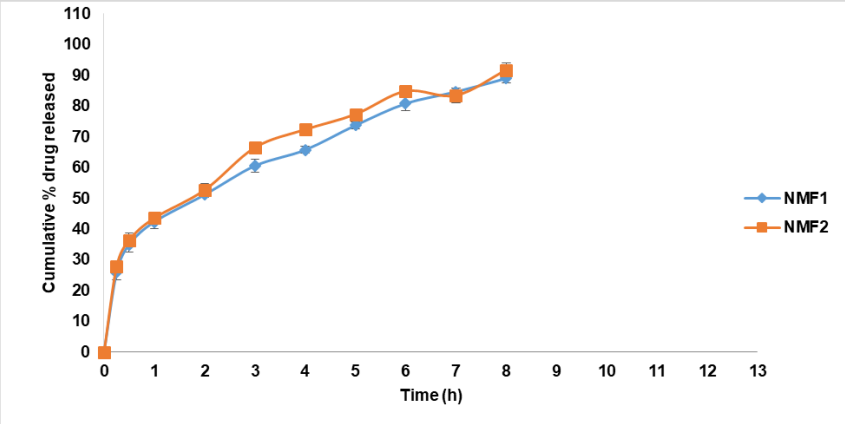

Fig. 4: Graph of *in vitro* drug release study of formulation NMF1-NMF2, Error bar indicates SD of n=3

% Cumulative drug release profile

Fig. 4 showed drug release of NMF1 and NMF2. Out of these two formulation NMF1 had the least amount of burst release, and NMF2 had the most. These two formulation showed corsmeyer peppas drug release with regression value 0.9942 and 0.9917 respectively.

Evaluation parameters of optimized batch of naproxen mcrosponge

FTIR

In FTIR analysis drug in alone and in combination with other excipients subjected for checking compatibility of drug other excipients. There is no appearance of new peak or disappearance of existing peak. IR spectrum of Naproxen showed absorption peak at 3214 cm^{-1} denoting O-H stretching of carboxyl group. Peak at 2900 cm^{-1} C-H stretch of aromatic ring and 1600 cm^{-1} due to stretching of C-H aliphatic stretching. The absorption peak at 1728 cm^{-1} were due to C=O stretch. Peak at 1000 cm^{-1} showed presence of ether moiety. According to FTIR spectra observations shown in fig. 4. Every characteristic peak of Naproxen was observed in the formulation spectra of physical mixtures and microsponges. Hence, Naproxen was shown by IR spectroscopy data to be stable in all microsponge formulations and compatible with specific polymers and excipients.

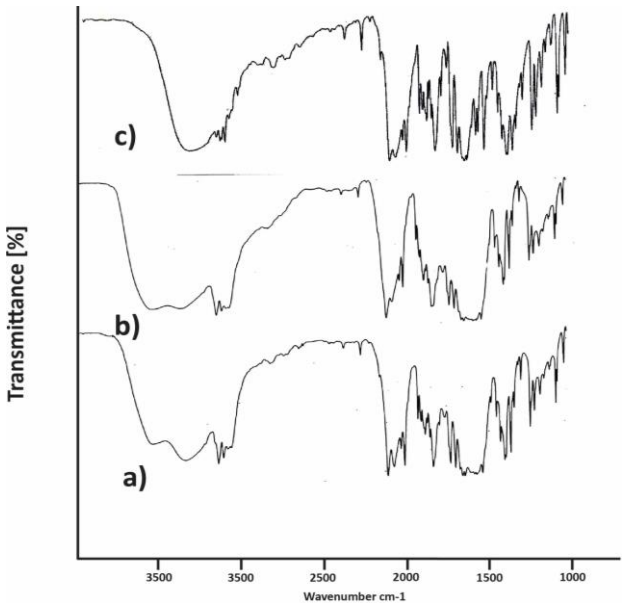

Fig. 4: IR spectra for a. Naproxen b. Naproxen and ethyl cellulose mixture c. Naproxen microsponges

SEM

SEM examination was performed on produced microsponges for the purpose of morphology and surface topography inquiries. Fig. 5 displays the microsponges' acquired SEM image. The microsponges that were generated were mostly spherical and very porous, according to the SEM data.

DSC

The DSC thermogram of pure drug and optimized formulation was presented in fig. 6. A prominent endothermic peak was detected at 150.14 C, which demonstrated the drug's crystalline nature. This endothermic peak with reduced intensity confirmed that no chemical interaction was seen in between drug and excipients during formulaion of microsponges.

XRD

The physicochemical properties of the prepared microsponges were to be assessed using the X-ray diffraction (XRD) method. Both Naproxen and its microsponge formulation showed sharp peaks at diffraction angle (2θ) 13 in their X-ray diffractograms. The crystalline character of the microsponges was indicated by the presence of peaks at the same diffraction angle as the Naproxen XRD pattern, but with slightly less intensity. The drug's crystalline state was partially preserved and was discovered to be thermally stable in the final formulation, according to XRD examination.

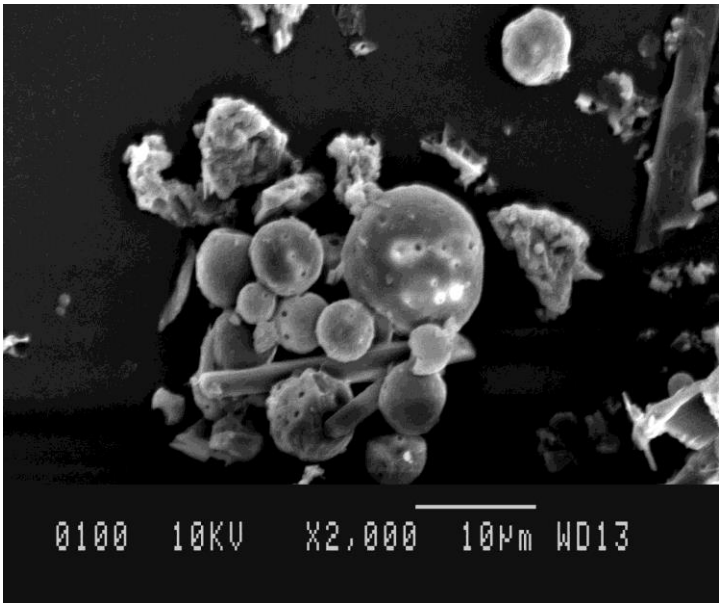

Fig. 5: SEM of naproxen microsponge

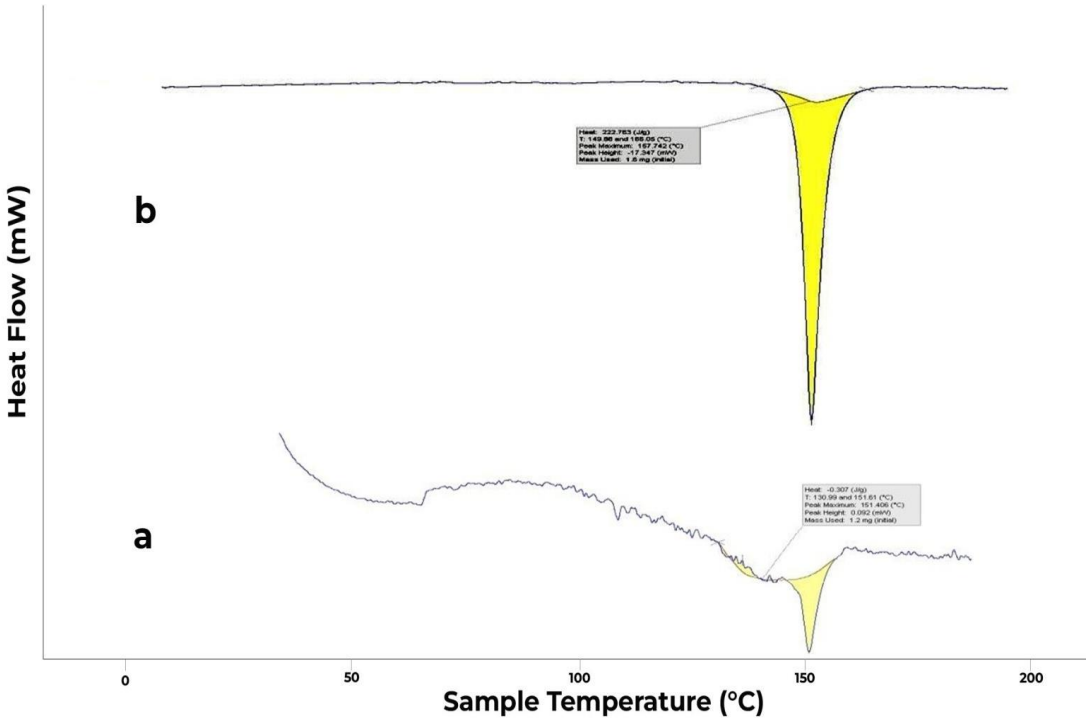

Fig. 6: DSC graphs for a. naproxen microsponges b. Naproxen

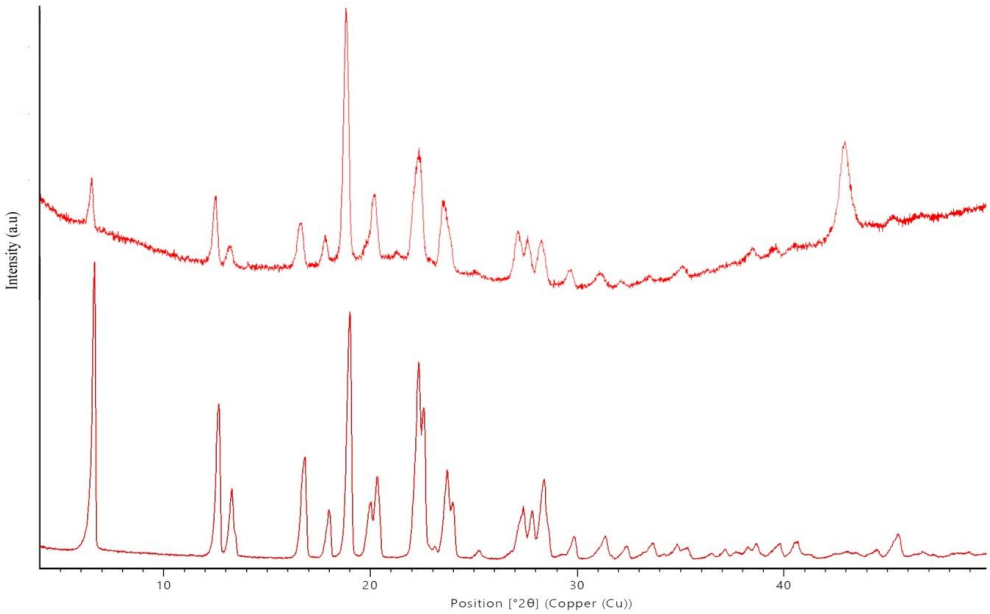

Fig. 7: XRD graphs of naproxen microsponges and naproxen

CONCLUSION

The goal of creating the Naproxen loaded microsponge drug delivery system was to increase the bioavailability, decrease the frequency for longer amount of time by quasi-emulsion solvent diffusion approach. BBD was used for preparation and optimization of various microsponges formulation. Comparative study of actual response and predicted response showed that NMF2 had minimum microsponge size and maximum drug release. The optimized formulation compatibility was confirmed by FTIR analysis, which revealed no chemical reaction between the material and polymer. Microsponges were reported to have a slightly spherical and rounded shape, and had Particle size less than 40 µm as revealed by SEM investigation. The DSC graph indicates that the microsponges formulation did not generate a sharp peak, indicating that the active component naproxen was entrapped in the polymer EC. The kinetic studies of NMF1 and NMF2 formulation were carried out and it was found that all the formulations followed corsmeyer peppas model.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

The work was carried out in collaboration between all the authors. Author Sonia Gupta conducted the formulation, optimization and evaluation activities and drafted the manuscript while Dr. Jyoti managed the analysis of the study and conducted literature searches. The article was read and approved by all the authors.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Kadhim ZM, Mahmood HS, Alaayedi MA, Ghareeb MM. Formulation of flurbiprofen as microsponge drug delivery system. Int J Pharmacol Res. 2020;12(3):748-53.
2. Jain V, Jain D, Singh R. Factors effecting the morphology of Eudragit S-100 based microsponges bearing dicyclomine for colonic delivery. J Pharm Sci. 2011;100(4):1545-52. doi: 10.1002/jps.22360, PMID 20960455.
3. D'souza JI, More HN. Topical anti-inflammatory gels of fluocinolone acetonide entrapped in eudragit based microsponge delivery system. Res J Pharm Technol. 2008;1(4):502-6.
4. Osmani RA, Aloorkar NH, Ingale DJ, Kulkarni PK, Hani U, Bhosale RR. Microsponges based novel drug delivery system for augmented arthritis therapy. Saudi Pharm J. 2015;23(5):562-72. doi: 10.1016/j.jsps.2015.02.020, PMID 26594124.
5. Rajab NA, Jawad MS. Formulation and *in vitro* evaluation of piroxicam microsponge as a tablet. Int J Pharm Pharm Sci. 2016;8(2):104-14.
6. Jangde R. Microsponges for colon targeted drug delivery system: an overview. Asain J Pharm Tech. 2011;1(4):87-93.
7. Amrutiya N, Bajaj A, Madan M. Development of microsponges for topical delivery of mupirocin. AAPS PharmSciTech. 2009;10(2):402-9. doi: 10.1208/s12249-009-9220-7, PMID 19381834.
8. EI-Houssieny BM, Hamouda HM. Formulation and evaluation of clotrimazole from pluronic for gels. J Drug Dis Ther. 2010;4:33-43.
9. Yadav V, Jadhav P, Dombe S, Bodhe A, Salunkhe P. Formulation and evaluation of microsponge gel for topical delivery of antifungal drug. Int J App Pharm. 2017;9(4):30-7. doi: 10.22159/ijap.2017v9i4.17760.
10. Gusai T, Dhavalkumar M, Soniwala M, Dudhat K, Vasoya J, Chavda J. Formulation and optimization of microsponge-loaded emulgel to improve the transdermal application of acyclovir-a DOE based approach. Drug Deliv Transl Res. 2021;11(5):2009-29. doi: 10.1007/s13346-020-00862-w, PMID 33159290.
11. Jelvehgari M, Siahi Shadbad MR, Azarmi S, Martin GP, Nokhodchi A. The microsponge delivery system of benzoyl peroxide: preparation, characterization and release studies. Int J Pharm. 2006;308(1-2):124-32. doi: 10.1016/j.ijpharm.2005.11.001, PMID 16359833.
12. Maiti S, Kaity S, Ray S, Sa B. Development and evaluation of xanthan gum-facilitated ethyl cellulose microsponges for controlled percutaneous delivery of diclofenac sodium. Acta Pharm. 2011;61(3):257-70. doi: 10.2478/v10007-011-0022-6, PMID 21945905.
13. Sodiyal N. Formulation and evaluation of ketoconazole loaded microsponge gel for topical drug delivery. World J Pharm Res. 2020;9(9):1060-9.
14. Lakshmi PK, Marka KK, Aishwarya S, Shyamala B. Formulation and evaluation of ibuprofen topical gel: a novel approach for penetration enhancement. Int J Appl Pharm. 2011;3(3):25-30.
15. Shahzad Y, Afreen U, Nisar Hussain Shah S, Hussain T. Applying response surface methodology to optimize nimesulide permeation from topical formulation. Pharm Dev Technol. 2013;18(6):1391-8. doi: 10.3109/10837450.2012.723721, PMID 22994526.
16. Pawar AP, Gholap AP, Kuchekar AB, Bothiraja C, Mali AJ. Formulation and evaluation of optimized oxybenzone microsponge gel for topical delivery. J Drug Deliv. 2015;2015(1):261068. doi: 10.1155/2015/261068, PMID 25789176.

17. Kshirasagar N, Puchchakayala G, KB. Comparative pharmacokinetic studies of marketed and microsponges gel loaded with diclofenac diethylamine in rabbits. Res J Pharm Technol. 2021;14(12):6385-91. doi: 10.52711/0974-360X.2021.01104.
18. Sareen R, Nath K, Jain N, Dhar KL. Curcumin loaded microsponges for colon targeting in inflammatory bowel disease: fabrication, optimization, and in vitro and pharmacodynamic evaluation. Biomed Res Int. 2014;2014(1):340701. doi: 10.1155/2014/340701, PMID 25093165.
19. Shuhaib B, Dr. Suja C. Formulation and characterization of topical gel containing microsponge of mefenamic acid. World J Pharm Life Sci. 2018;4(2):109-19.
20. Syed SM, Gaikwad SS, Wagh S. Formulation and evaluation of gel containing fluconazole microsponges. Asian J Pharm Res Dev. 2020;8(4):231-9.
21. Jain V, Singh R. Development and characterization of eudragit RS 100 loaded microsponges and its colonic delivery using natural polysaccharides. Acta Pol Pharm. 2010;67(4):407-15. PMID 20635537.
22. Kiliçarslan M, Baykara T. The effect of the drug/polymer ratio on the properties of the verapamil HCl loaded microspheres. Int J Pharm. 2003;252(1-2):99-109. doi: 10.1016/s0378-5173(02)00630-0, PMID 12550785.
23. Priyanka NV, Neeraja P, Mangilal T, Kumar MR. Formulation and evaluation of gel loaded with microspheres of apremilast for transdermal delivery system. Asian J Pharm Clin Res. 2019;7:411-7. doi: 10.22159/ajpcr.2019.v12i2.29374.
24. Thavva VE, Baratam SR. Formulation and evaluation of terbinafine hydrochloride microsponge gel. Int J App Pharm. 2019;11(6):78-85. doi: 10.22159/ijap.2019v11i6.32502.
25. Zia RA, Nazir AK, Khan MK, Maan AA, Rashid AY. Preparation of ascorbic acid and cholecalciferol microsponges for topical application. Int J Pharm Pharm Sci. 2017;9(10):280-7. doi: 10.22159/ijpps.2017v9i10.17525.
26. Rajeswari S, Swapna V. Microsponges as a neoteric cornucopia for drug delivery systems. Int J Curr Pharm Sci. 2019;11(3):4-12. doi: 10.22159/ijcpr.2019v11i3.34099.