RESEARCH ARTICLE

Indomethacin-Loaded Nanosponges for Oral Delivery: Formulation Strategy, Optimization, and *In-vitro* Evaluation

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ABSTRACT

Chronic illnesses like arthritis cause pain and inflammation, requiring extended oral analgesic therapy. To reduce adverse reactions, active pharmaceutical ingredients are administered through sustained-release dosage forms. However, methods like matrix tablets, osmotic systems, and ion exchange resins have limitations. Nanotechnological approaches like nanosponges improve precision and accuracy in medication release manufacturing. Encapsulated formulations offer benefits like reduced side effects, varied dose options, non-irritating properties, and aesthetic appeal. Nanosponges are used in formulation to provide stability, improve bioavailability, alter taste, and target medication distribution systems. β-cyclodextrin-based nanoparticles are used to achieve active pharmaceutical ingredients characteristics. Polymers like ethylcellulose are commonly used for sustained-release formulations. Nanosponges can be synthesized using techniques like solvent technique, cross-linking, ultrasound-assisted preparation, and emulsion solvent diffusion. Ultrasound-assisted method is efficient and cost-effective. The study aims to develop indomethacin-loaded nanoparticles for a sustained-release tablet, obstructing prostaglandin synthesis, a chemical responsible for inflammation and discomfort. Indomethacin, a class II medication, is suitable due to its low solubility and molecular weight.

This study developed and evaluated sustained release preparations of indomethacin-incorporated nanoparticles using EC as a polymer, analyzed physicochemical parameters, and developed a nanoparticle-loaded tablet dosage form.

Keywords: Gout, nanosponges, Indomethacin, sustained-release, β-cyclodextrin, ultrasound-assisted method.

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INTRODUCTION

Chronic illnesses, including arthritis, are related to considerable pain and inflammation, requiring extended oral analgesic therapy. Extended analgesic use might result in several adverse consequences, including gastrointestinal inflammation, perhaps leading to a gastric ulcer.[1] The administration of active pharmaceutical ingredients (API) through sustained-release dosage forms is an optimal method for reducing adverse reactions.[2] Various methods, including matrix tablets, osmotic and gastroretentive systems, and ion exchange resins, can modify drug release from the dosage form. However, these methods have limitations such as stability issues, dose toxicity, gastric irritation, acidic pH instability, high costs, and limited dose modification in ion exchange resin components.[3]

The focus has shifted to nanotechnological approaches like nanosponges to improve the precision and accuracy of medication release manufacturing.[4]

Nanospheres are small, spherical, and porous polymeric delivery systems that distribute medication in a more predictable and controlled manner.[5] Encapsulated formulations offer numerous benefits, such as reduced side effects, varied dose options, non-irritating properties, and enhanced aesthetic appeal, making them a popular choice for sustained-release preparations, delivering a diverse range of drugs.[6]

In numerous instances, NS provides stability to the preparation by safeguarding against premature degradation of the medication. Improvement of bioavailability, alteration of taste, and targeted medication distribution systems are additional focal points for formulation scientists, whereby β-cyclodextrin (CD)-based nanoparticles have effectively been employed to attain the requisite characteristics of active pharmaceutical ingredients (APIs).[7] A range of polymers, including hypercross-linked dichloromethane, ethyl cellulose, may be utilized to produce nanostructures. Between these, ethylcellulose is the most often utilized polymer for sustained-release formulations.[8] Numerous instances in the literature demonstrate the efficient application of these polymers in the preparation of sustained-release

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Table 1: Investigating ranges of variable for Xanthan gum & PVP K-30

Sr. No.	Factor	Low level	High level
A	Xanthan gum	28	56
B	PVP K-30	6	12

formulations, such as oral and topical dose forms of artesunate and lansoprazole.[9]

Nanosponges can be synthesized using several techniques, including the solvent technique, cross-linking of β-cyclodextrins, ultrasound-assisted preparation, as well as the emulsion solvent diffusion approach.[10] The ultrasound-assisted synthesis method is an efficient, time-saving, and cost-effective approach for the synthesis of nanosponges.[11] They are typically assessed for their physiochemical and structural analysis properties of medication. Drug particles for nanosponges must have specific features for effective entrapment. Nanocavities can effectively sequester molecules with a molecular weight between 100-400 Daltons and less than five condensed rings, resulting in high entrapment efficiency.[12]

Indomethacin is a type of NSAID used to treat arthritis, pain, and inflammation.[13] The present study aimed to develop indomethacin-loaded nanoparticles for the formulation of a sustained-release tablet. It obstructs the synthesis of prostaglandins, which are chemicals responsible for inflammation, rigidity, and discomfort.[14] Conventional therapy necessitates prolonged multiple dosages, resulting in many side effects, including gastrointestinal discomfort, bleeding, perforation, and ulceration. Indomethacin, a class II medication with a molecular weight of 357.79 g/mol, is suitable for investigations due to its low solubility and low molecular weight.[15]

The objective of this work was to formulate and assess sustained release preparations of indomethacin-incorporated nanoparticles utilizing EC as the polymer. The preparations were analyzed for multiple physicochemical parameters as well as evaluated for medication distribution using *in vitro* techniques. Finally, a nanoparticle-loaded tablet dosage form was developed and assessed for its formulation characteristics.

MATERIALS AND METHODS

Materials

Indomethacin was graciously supplied by FIS- Fabbrica Italiana Sintectici S.p.A. Ethyl cellulose (EC), dichloromethane (DCM), and methanol of analytical grade were acquired from S. D. Specialty chemicals.

Methods

Preparation of IND-loaded NS

Table 3: Process parameters for preparation of the Placebo

Ratio	1:1	1:2	1:3	1:4	1:5
β-cyclodextrin (gm)	1	1	1	1	1
Dichloromethane (ml)	0.75	1.50	2.25	3.00	3.75

Part 1: Preparation of Placebo

The ultrasound-assisted synthesis technique was employed to formulate IND-loaded NS. Placebo was prepared by utilizing a specific ratio (1:2) of polymer (β-cyclodextrin) and cross-linker (dichloromethane). This included 1 gram of β-cyclodextrin and 1.50 ml of dichloromethane. Initially, the polymer was combined with a cross-linking agent in a flask. It was thereafter immersed in an ultrasonic bath containing water heated to 90°C. The material was crushed, ethanol was employed for Soxhlet extraction to eliminate impurities and polymer, and the final resulting substance was filtered and dried.

Part 2: Loading of the Drug in the Placebo

The medication was loaded into the nanosponges utilizing a mechanical stirrer. The drug and placebo were combined with a methanol-water mixture, stirred for four to five hours to improve medication loading, filtered via Whatman filter paper, and dried. The formulations were sealed, stored in a desiccator, and characterized after drying. The mixture was then filtered and dried before being used for further study.

Characterization of Indomethacin-loaded Nanosponges

The formulated preparations were assessed based on several physicochemical properties, including yield percentage, drug loading, as well as particle size. A structural examination was conducted.

Assessment of % Yield, Drug Loading, Particle Size

The parameters were determined by calculating the initial weight of the solid materials used and the total weight of the produced dry nanosponges using a formula as given below equation 1.

$$Percentage\ Yield = \frac{Actual\ Yield}{Theoretical\ Yield} x100 \quad \text{--- (1)}$$

Percent drug loading was evaluated using equation 2.

$$Drug\ loading = \frac{Drug\ content\ of\ NS}{Weight\ of\ NS\ recovered} x100 \text{ -- (2)}$$

Morphological Analysis

Morphological investigations of particular NS formulations were performed utilizing scanning electron microscopy (JSM-5200, Tokyo, Japan) integrated with an automated imaging system. Differential scanning calorimetric tests were conducted on pure drug, polymer (cyclodextrin), a mixture of drug and polymer, and drug nanosponges to evaluate changes during nanosponges production and

Table 2: Composition of Indomethacin Nanosponges Tablet

Ingredient	Quantity in batch (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Indomethacin nanosponges	120	120	120	120	120	120	120	120	120
Xanthan gum	28	42	56	28	42	56	28	42	56
PVP K-30	6	6	6	9	9	9	12	12	12
Lactose	13	13	13	13	13	13	13	13	13
Magnesium stearate USP/NF	1	1	1	1	1	1	1	1	1
Isopropyl alcohol 99%	Quantity Sufficient (QS)								

Table 4: *In-vitro* dissolution of Indomethacin nanosponges for F1-F4 batch

Time (min)	% Drug release of nanosponges			
	F1	F2	F3	F4
0	0	0	0	0
5	10.56	13.89	17.76	15.76
10	29.78	32.78	34.89	36.55
15	39.89	43.56	49.78	51.65
30	55.76	62.54	69.56	71.65
45	78.98	81.67	86.75	85.78
60	89.76	95.43	98.67	92.56

enhance drug solubility. Thermal curves were obtained using a DSC 60 at a temperature rate of 10°C/min in a nitrogen environment. Powder samples of the pure medication, polymers, and particular nanostructured formulations were examined utilizing an X-ray diffractometer. The Fourier transform infrared (FTIR) analysis of materials was conducted using the Agilent Technologies Cary 630 FTIR spectrophotometer. The spectra of nanosponges were captured and examined within the limit of 4000 cm^{-1} to 650 cm^{-1}.

In-Vitro Drug Dissolution Release Study

The study used USP type II instrument to perform a study on powdered Nanosponges preparation samples. The dissolution media was 900 mL of phosphate buffer (pH 7.2), and samples were extracted and replaced with new, warmed media. The specimens were strained and evaluated using a standardization curve with a R^2 value of 0.998 at λmax 317 nm.

Experimental Design

A factorial design is a technique employed to assess two or more elements concurrently, facilitating the simultaneous evaluation of the effects of many components and their interactions. Factors may be qualitative or quantitative, with their levels representing the values or designations attributed to them. Factorial trials encompass every possible combination of all levels across all factors. The effect of a factor refers to the alteration in reaction resulting from modifications in the level(s) of that factor. The optimization of pharmaceutical formulations is essential for formulation research, with the aim of creating a mathematical model that characterizes the reactions. The research employed Design Expert® software for a systematic examination of polymer combinations through a two-factor three-level complete factorial design. Polynomial models for all response variables were developed by running a regression function, with statistical validity confirmed using ANOVA. The ideal mathematical prototype was chosen based on many statistical metrics, like the coefficient of variation, multiple correlation coefficient and so on.

The current study sought to develop an optimum formulation for Indomethacin nanosponges by assessing the impact of various factors and their interactions during the production process. Concurrently, the nanosponges were undergoing processing; the influence of various factors was assessed by altering their quality and quantity. Ultimately, both of the most critical components were identified as independent factors. In the subsequent stage, to ascertain the low and high amounts of each factor, several formulations were developed, and the findings are presented in Table 1.

Table 5: Post compression evaluation of Tablet formulations

Batch	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)
F1	0.168± 0.001	3.7	0.51	3.10± 0.014	98.40
F2	0.182± 0.002	4.0	0.55	3.10± 0.012	96.13
F3	0.196± 0.002	3.9	0.60	3.20± 0.016	99.54
F4	0.171± 0.001	4.0	0.55	3.12± 0.012	97.73
F5	0.185± 0.003	4.1	0.62	3.15± 0.020	95.58
F6	0.199± 0.001	4.2	0.63	3.20± 0.024	95.22
F7	0.174± 0.003	4.3	0.65	3.25± 0.018	94.74
F8	0.188± 0.002	4.4	0.55	3.30± 0.010	93.09
F9	0.202± 0.002	4.5	0.61	3.10± 0.012	93.85

Table 6: *In-vitro* dissolution of Indomethacin nanosponges tablet for F1-F9 batch

Time (hr)	Percentage drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	1.875	5.625	16.625	3.000	4.500	15.750	5.875	15.750	16.625
2	5.635	15.531	23.342	19.517	19.525	19.588	15.783	19.838	18.967
3	18.156	25.983	31.129	36.483	29.358	33.858	28.337	36.485	31.105
4	33.976	34.672	41.885	41.915	41.788	50.188	36.282	48.840	38.172
5	41.813	45.997	49.444	50.232	48.931	54.653	42.063	54.633	44.711
6	49.606	56.817	54.148	57.278	54.771	59.677	45.233	60.927	54.372
7	54.649	60.254	61.049	66.817	65.928	65.955	54.500	74.837	62.676
8	60.927	65.156	68.713	72.369	72.490	69.740	61.426	82.414	68.722
9	67.337	76.935	74.005	79.763	79.651	79.260	72.465	92.081	78.130
10	74.122	85.12	81.034	85.066	86.940	88.063	81.276	95.009	84.932
11	86.535	92.057	92.073	92.183	94.981	92.487	92.074	96.275	90.719
12	95.603	96.884	99.884	95.010	97.525	93.636	95.259	94.657	96.376

An experimental grid was created utilizing the 3^2 factorial design with two variables, employing the Design Expert 7.0.0 software, resulting in the execution of 9 experiments. The effect of xanthan gum concentration on drug release, drug content, and tablet hardness is shown by the 3D surface chart. First, a higher xanthan gum concentration increases drug release; above a certain threshold, nevertheless, additional concentration reduces % drug release, suggesting a notable impact of factor A on drug release behavior. In a similar vein, the drug content exhibits a positive association with xanthan gum concentration, therefore indicating that factor A clearly influences drug content. Furthermore, underlining the significant influence of component, A on the formulation characteristics, tablet hardness rises as the xanthan gum content increases. These results emphasize the critical part xanthan gum concentration plays in controlling formulation drug release, content, and hardness. For IND nanosponges, F3 batch was optimised batch on the basis of particle size (lowest), drug release (highest), zeta potential (stable) and drug content (highest). This batch was further used to prepare the naosponge tablet. (F1 to F9). From the drug content, drug release and hardness: F3 batch of nanosponge tablet was found to be optimized.

Manufacturing of Nanosponges Tablets

Tablet with medication-incorporated nanosponges were produced via the direct compression technique. The ratio of nanosponges that produced optimal outcomes in solubility and dissolution testing was selected for formulation. Indomethacin nanosponges were employed in the formulation of the tablets. Xanthan gum helps to control drug release by forming gel matrix. PVP K-30 is used as binder, lactose acts as filler, magnesium stearate works as a lubricant and Isopropyl alcohol is solvent in nanosponges tablet preparation. The detailed composition of the tablets can be found in the table 2 below.

Manufacturing the Tablet using the Direct Compression Method

The tablet components underwent sieving using sieve no. 60. The drug (Indomethacin) was maintained at a constant amount of 120 mg in all 9 nanosponges batches. Next, the excipients, such as Xanthan Gum, PVP-K 30, Lactose,

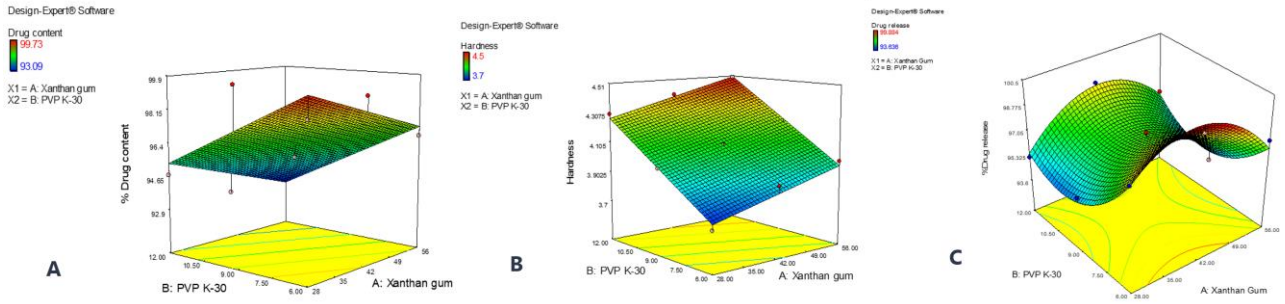

Figure 1: (A) 3D Surface Plot of % Drug Content of Indomethacin with respect to Xanthan gum and PVP K-30, (B) 3D Surface Plot of Hardness of Indomethacin with Respect to Xanthan gum &PVP K-30, (C) 3D Surface Plot of % Drug Release of Indomethacin with Respect to Xanthan gum and PVP K-30

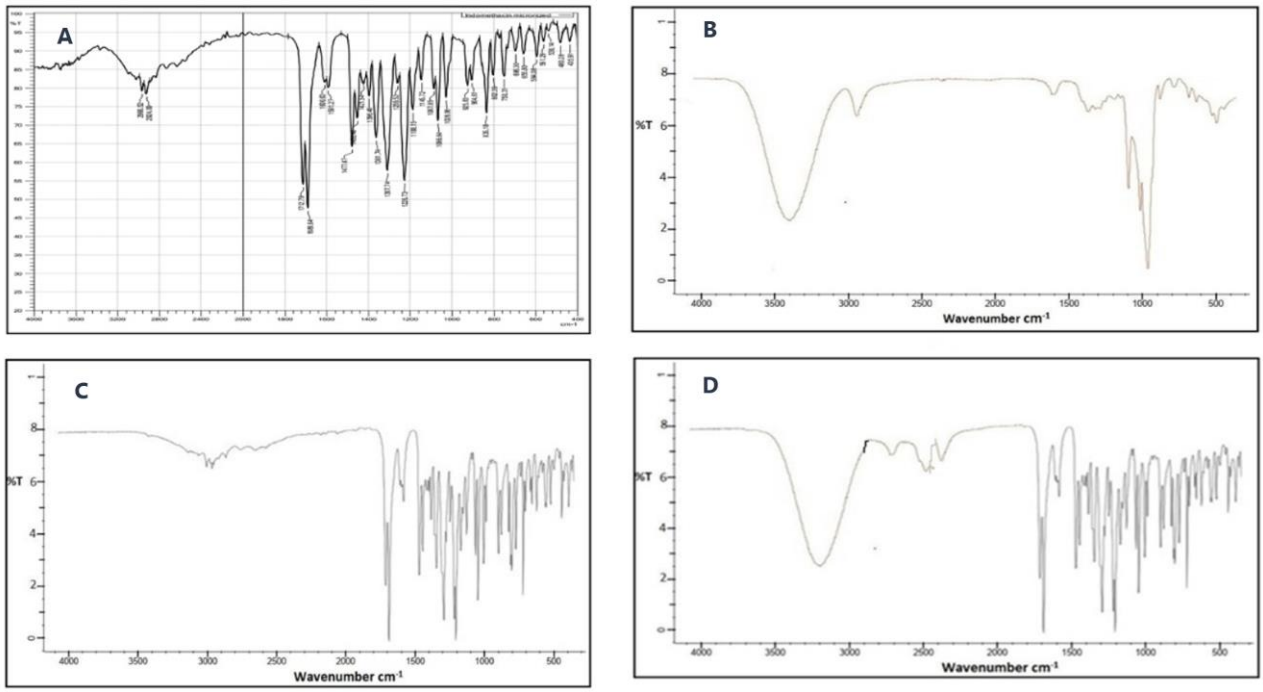

Figure 2: FTIR Spectra of Indomethacin(A), Pure Indomethacin and Beta Cyclodextrin (B), Beta-Cyclodextrin(C), Indomethacin Nanosponges (D).

Table 7: Model fitting of optimize batch of Indomethacin formulation

Run	Zero order	1st order	Higuchi	Korsmeryspeppas
(R^2)	0.993	0.8214	0.9875	0.9866

Table 8: Stability study of Optimized formulation

Time (day)	Drug content (%)	*In vitro* drug release (%)
0	99.13	99.884
30	97.52	96.522
60	95.61	93.548
90	88.32	91.365

Magnesium Stearate, and Isopropyl Alcohol, were precisely weighed according to the details in table 2. Subsequently, all the powders were blended using geometric dilution. The ingredients mentioned above were compacted into tablets using a 10 mm punch on a rotary tablet minipress.

RESULTS AND DISCUSSIONS

Manufacturing and Assessment of NS Preparations

They can be synthesized by multiple techniques, including solvent emulsion, solvent diffusion, and ultrasound-assisted processes. The choice of technique is contingent upon the specific medication and polymer utilized. The ultrasound-assisted synthesis methodology is a straightforward and economical method suitable for medicines with low aqueous solubility. This study employed this strategy because to the IND's classification as a BCS (Biopharmaceutical Classification System) class II medication, characterized by limited water solubility.

The ultrasound-assisted synthesis method prepared IND-loaded nanosponges (NS) using a 1:2 ratio of β-cyclodextrin and dichloromethane. Different placebos were prepared using different polymers and cross-linkers. All the placebos were observed under a Motic microscope for nature and particle size. From the above observation, it was concluded that β-cyclodextrin polymer and dichloromethane were best suited for further formulation and evaluation because of their spongy nature and particle size in nm. The polymer mixed with the cross-linker was heated, ground, and extracted. Drug loading involved mixing with methanol-water and stirring for 4–5 hours before filtering and drying. Formulations were stored in closed containers.

Results of entrapment efficiency and medication loading showed that these parameters are dependent on formulations with an equivalent medication to ethyl cellulose ratio (i.e., F4 & F3), elevated values for these parameters are seen. Hence, the medication quantity per element of polymer is a significant element in this context. These findings contradict with earlier investigations, which indicated that larger drug-to-polymer ratios led to enhanced entrapment efficiency and drug loading.

The percentage yield of the produced formulations was similarly reliant on the drug-to-polymer ratio. The parameter values for NS formulations ranged from 20% to 51%. The poor % yield numbers may be attributed to the adhesive properties of the manufactured product. A segment of the product adhered to the apparatus due to aggregation, and foaming led to a reduction in percent yield. Zeta potential quantifies the surface charge and is a critical determinant of nanoparticle stability. Our results indicate that all created formulations display Zeta potential values ranging from -11 to -17 mV, signifying stable formulations.

Structural Analysis

The analysis focused on optimized batches of IND, polymers, and NS formulations. The FTIR spectra showed characteristic peaks for amide, amine, and C-O in unadulterated IND spectra. β-cyclodextrins also displayed these peaks. Some NS formulations showed an expansion of drug peaks due to medication encapsulation within the NS core. A notable feature was a 1680 cm-1 peak at 1680 cm-1, attributed to the amide group of IND involved in hydrogen bonding. No alteration was observed in NS spectra, indicating no interaction between medication and polymer.

In-Vitro Dissolution Release Studies

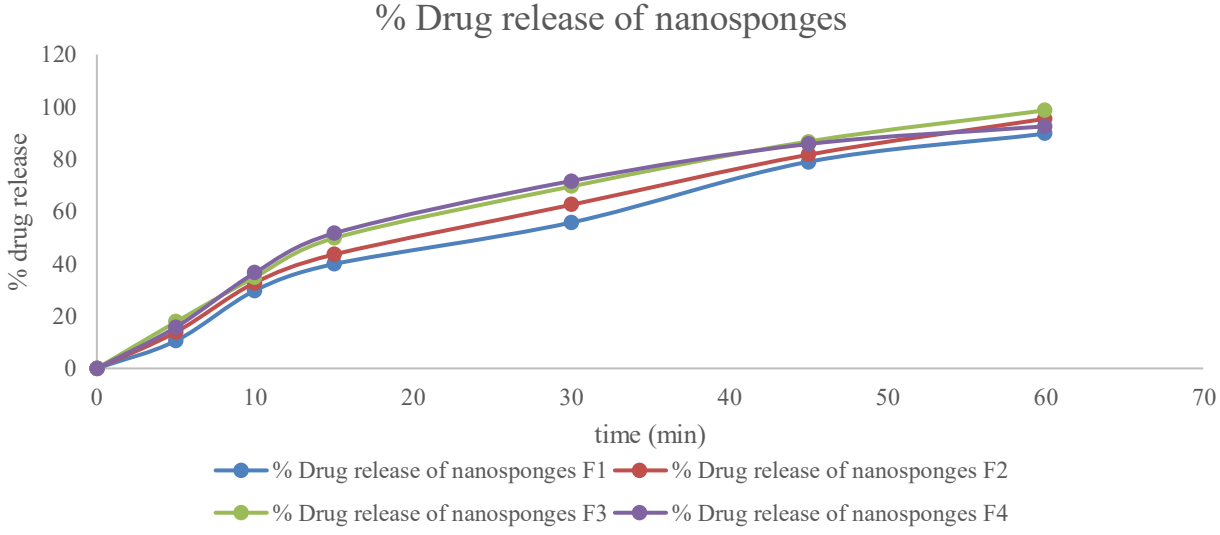

Figure 3: *In-Vitro* Drug Release of different batches

This test was conducted for 1 hour using phosphate buffers at pH 7.2 and pH 6.8. The dissolving profile of formulations F1 to F4 indicates that batch F3 of Indomethacin exhibits a superior drug release characteristic compared to the other formulations. The total percentage release is presented as a mean of 3 formulations. The total percentage of medication for all batches is presented in Table 4 and Figure 3 below.

Evaluation of NS Tablets

Pre-compression Analysis

All formulation mixtures underwent assessment of different parameters. The analysis of nanosponges and their combinations with various formulation elements shows improved flow characteristics and moderate to good compressibility, enabling direct tablet compression and ensuring optimal flow from the hopper with uniformity in final tablets.

Post-compression Analysis

The tablets were subjected to multiple post-compression evaluations, including checking for friability and content homogeneity, to ensure their quality. All metrics were within the limitations specified in USP 30 (2007). The tablets met the official standards for durability (0.6% friability), strength (3.9 kg/cm≤ hardness), and size (3.20±0.016 mm thickness). The drug content was measured at 98.62% for pure drug tablets and 99.54% for NS tablets. The post-compression analysis of tablet preparations is presented in Table 5.

Dissolution Studies of Prepared Nanosponges Tablets

A 5 milliliter sample was extracted and replaced with dissolution fluid to maintain consistency. The specimens were spectrophotometrically analyzed at 317 nm for indomethacin, and the amount of drug release was determined using calibration curves, with dissolution investigations performed in triplicate.

In-Vitro Drug Release Study of Indomethacin Nanosponges Tablets

The slope of R^2 indicated that the medication release profile of the modified batch adhered to zero-order kinetics, as demonstrated in Table 7.

Stability Studies

The optimized formulation underwent stability tests according to ICH requirements, examining parameters like drug amount and *in vitro* drug release before, during, and after 30-60 days of stability. Results showed no significant changes, indicating the batch is stable and not significantly affected by high humidity and temperature conditions.

CONCLUSION

A sustained release tablet of IND was developed using nanoscale particles (NS) made of EC, using the ultrasound-assisted method. The drug-polymer ratio is crucial for nanoparticle formulations. The nanoparticles have a spherical morphology and a porous structure. The sustained release profile was validated using *in-vitro* drug release, which proved more accurate. NS pills were developed as the final dose form, adhering to official limits. The NS-based method is considered more suitable for drug tablet development. Future bioavailability studies using animal models may be conducted to predict the pharmacokinetic profile.

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