# SYNTHESIS AND APPLICATION OF THIOLATED SODIUM ALGINATE FOR FORMULATION OF MUCOADHESIVE MICROPARTICULATE DRUG DELIVERY SYSTEMS OF ETORICOXIB

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**Abstract:**
The effectiveness of mucoadhesive drug delivery systems relies on the choice of the polymer, which typically adheres upon hydration. Selected polymers must maintain their adhesion to biological membranes and retain the drug for extended periods. Most hydrophilic polymers form weak non-covalent bonds, hindering the precise localization of dosage forms at target sites, resulting in suboptimal therapeutic outcomes. This limitation can be overcome by modifying natural polymers with thiol groups, known as thiomers. Thiomers offer enhanced stability across a wide pH range and prolonged residence at the intended targets.The primary objective of this study was to synthesize and characterize thiolated sodium alginate (TSA). Subsequently, etoricoxib-loaded microspheres were formulated using TSA, and the manufacturing process was optimized. The optimized formulation, denoted as MM-TSA, demonstrated complete and controlled drug release at the conclusion of dissolution testing. Cell viability assays confirmed the safety of both thiolated sodium alginate and the formulated microspheres. Furthermore, TSA exhibited significant mucoadhesive strength. These findings endorse S-protection as a promising strategy for enhancing the absorption of poorly water-soluble drugs like etoricoxib.

**Keywords:** - Etoricoxib, Sodium alginate, Thiolation, Mucoadhesion, Microspheres.

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## 1. Introduction:

Microspheres, often referred to as microencapsulation or microparticles, are a class of drug delivery systems that have garnered significant attention in recent years for their potential to improve the therapeutic efficacy and safety of various pharmaceutical agents. These minute spherical particles, typically ranging in size from a few micrometers to a few hundred micrometers, offer a versatile platform for drug encapsulation and controlled release, making them a promising tool in the field of pharmaceutical research and development. Microparticles' sizes range from 1 to 1000 μm and the well-known matrix or reservoir structure they exist in have various different structures [1-3]

Apart from the choice of excipients, the structure and shape of drug delivery systems play a crucial role in their functionality. Multiparticulate drug delivery systems, which encompass micropellets, microgranules, microspheres, microcapsules, microsponges, and liposomal preparations, have gained significant attention due to their diverse and advantageous technological characteristics. The unique characteristics of microspheres make them well-suited for a wide range of applications, including the delivery of drugs with varying physicochemical properties, such as poorly water-soluble compounds or those with a short half-life in the body. One of the key advantages of microspheres is their ability to modulate the release of the encapsulated drug, enabling precise control over drug pharmacokinetics and pharmacodynamics. This control can result in a more sustained and targeted release of therapeutic agents, ultimately leading to improved patient compliance and reduced side effects [4,5]. Microspheres can be formulated from a variety of biocompatible and biodegradable materials, such as polymers, lipids, and proteins, allowing for tailored drug release profiles and compatibility with different administration routes. This versatility extends their potential applications to oral, parenteral, transdermal, and inhalation routes, among others

In the 1980s, the idea of mucoadhesion and mucoadhesive polymers came up. They were an interesting way to send drugs to specific body sites or absorption windows. They stick to nasal membranes when they come in contact with moisture because they are made of polymers that stick to surface. This makes touch with the mucosa last longer and keep happening, which increases the time the drug stays in the right place. [6]. Some mucoadhesive stomach systems have worked well, but they still haven't reached their full potential. Previous generations of mucoadhesive polymers had some good results, but they weren't able to stick well to the digestive system because they relied too much on weak hydrogen bonds, ionic interactions, and Van der Waals forces. As a result, they couldn't be sure that the dose forms were placed correctly.[7,8]. Thiolated polymers are one of the new viable mucoadhesive polymers [9] that have shown to be a favourable type of polymer excipients. Thiomers, as opposed to traditional polymers, exhibit superior capabilities by establishing robust molecular connections via thiol/disulfide exchange reactions with membrane subdomains abundant in cysteine[10]. According to the given criteria, thiomers allow dose forms to stay in one place for a long time while also being biodegradable

The emergence of a new generation of NSAID treatments that selectively target cyclooxygenase-2 (COX-2) while sparing COX-1 provides an alternative therapeutic option for many RA patients and individuals with other inflammatory disorders [11]. Previous studies have demonstrated the effectiveness and favorable tolerability of selective COX-2 inhibitors like rofecoxib and celecoxib as treatments for RA. These drugs have shown a reduced risk of gastrointestinal toxicity compared to nonselective NSAIDs [17,18]. A recent clinical trial conducted in the United States investigated the use of the highly selective COX-2 inhibitor etoricoxib (at a dose of 90 mg) for the treatment of RA.The current work seeks to synthesize and apply thiolated sodium alginate (TSA) to formulate mucoadhesive microparticles loaded with etoricoxib.

## 2. MATERIALS AND METHODS

### *Materials*

Etoricoxib was generously provided as a gift sample by Dr. Reddy's Laboratories located in Ahmadabad, India. Sodium alginate was sourced from Yarrow Chemicals in India, while chitosan RS100 was obtained from Sigma Aldrich. All other necessary chemicals were acquired from local suppliers.

### Preparation of thiolated sodium alginate (TSA)

To prepare the thiolated polymer, an initial step involved dissolving 2 grams of pure sodium alginate in 50 mL of deionized water. Subsequently, a solution containing 50 mM of EDAC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) and 4 grams of thioglycolic acid

was added to the sodium alginate solution. The resulting reaction mixture was allowed to sit undisturbed at room temperature for 3 hours.Following this, the reaction mixture was placed into a dialysis membrane and dialyzed through several steps. It was first dialyzed against 5 mM hydrochloric acid (HCl) at 10 ± 1 °C for 1 hour, then against 5 mM HCl containing 1% sodium chloride for 2 hours at room temperature, and finally against 1 mM HCl containing 1% sodium chloride for an additional 2 hours at room temperature.After the dialysis steps, the reaction mixture was collected and subjected to lyophilization using an Allied frost apparatus at -30 ± 1 °C under a pressure of 10.01 mbar. The resulting material was stored at +4 °C.

**Evaluation of thiolated sodium alginate (TSA)**
**Thiol content**
The degree of thiol group substitution was determined using Ellman's reagent [13]. Initially, a precisely weighed amount of thiolated gum ghatti (50 mg) was dissolved in 25 ml of water. A 2.5 ml aliquot was taken from this prepared solution and then diluted with 2.5 ml of 0.5 M phosphate buffer (pH 8.0). This mixture was allowed to react with 5 ml of Ellman's reagent over a period of two hours.Following the reaction, the absorbance of the resulting mixture was measured using a UV spectrophotometer at 450 nm. The total number of thiol groups was determined using a standard curve created with thioglycolic acid and Ellman's reagent.

**Viscosity**
The rheological properties of both gum ghatti and thiolated gum ghatti were assessed using a rheometer (MCR 92, Anton Paar, Austria). In the temperature sweep analysis, the samples were tested over a temperature range from 20 °C to 60 °C, with a constant shear rate of 10 s^-1 and a heating rate of 2 °C/min.Furthermore, a shear rate sweep analysis was conducted over a range from 0.1 to 1000 s^-1 to evaluate the flow behavior. Data was collected over a duration of 30 seconds on a logarithmic scale, and the measurements were carried out at a constant temperature of 25°C [14].

**Characterization of SA and TSA**
SA and TSA were characterized by FTIR, XRD and rheological studies.

**Assessment of mucoadhesion potential of GG and TGG**
The mucoadhesive property of the SA and TSA was compared with chitosan through *in vitro*and *ex vivo* methods like Mucoadhesion studies via rotating cylinder, Shear stress measurement, Wilhelmy's method, Falling sphere method, Detaching force measurement apparatus.

**Formulation of gastro retentive microspheres using TSA**
The measured amount of thiolated sodium alginate (TSA) was dissolved in 50 ml of freshly prepared 1M sodium hydroxide solution. Using a mechanical stirrer, the solution was agitated for 15 minutes to ensure a homogeneous mixture. An appropriate quantity of glibenclamide was dispersed into the resulting solution. Subsequently, a required amount of sodium trimetaphosphate was added and continuously stirred for an additional 15 minutes.The resulting dispersion was slowly expelled drop by drop using a syringe into preheated corn oil, with a magnetic stirrer in place to prevent droplet accumulation. To further avoid droplet aggregation, an adequate amount of surfactants, such as Span 80 and Tween 80, was introduced into the corn oil.The resulting microspheres were then separated through centrifugation, followed by filtration and cleaning with propanone to remove any excess corn oil. The isolated microspheres were air-dried for a period of 48 hours [15].

***Optimization using response surface methodology and various statistical applications.***
The process parameters chosen were TSA ($X_1$) concertation and stirring speed ($X_2$) at five stages coded as -1.414, -1, 0, +1, and +1.414. These variables were standardized for entrapment efficacy (EE) ($Y_1$) and in vitro mucoadhesion nature ($Y_2$). Design Expert V.12 was used to implement the central composite model, providing 15 experimental trials. Table 1, depicts the entire work plan interns of coded and real values of selected variables and restrains of dependent factors [16]. Quadratic regression was applied to measure the response in every trial, and an investigation was performed.

**Table 1.** Total work plan interns of coded and real values of selected parameters and constraints of dependent factors for central composite design.

| Selected formulation factors | Levels | | | | | Responses/Dependent Variables | Constraints |
|---|---|---|---|---|---|---|---|
| | **-1.414** | **-1** | **0** | **+1** | **+1.414** | | |
| Concentration of TSA (%)-$X_1$ | 1.189 | 0.1.5 | 2.25 | 3 | 3.310 | EE (%) | Maximum |
| Stirring speed(rpm)- $X_2$ | 177.157 | 250 | 425 | 600 | 672.487 | In vitro mucoadhesion (%) | Maximum |

**Evaluation of trial batches**

***EE***

The formulated microspheres (50 mg) were broken in a glass mortar, and the powder was dispersed in SGF (pH 1.2). The obtained solution was subjected for sonication around half an hour in bath sonicator and left overnight [17]. Following 24 h, filtration was done and spectrophotometry studied of the filtrate was performed at 233 nm. The entrapment efficiency can be determined using the formula;

EE = practical drug content / theoretical drug content × 100

***In vitro mucoadhesion test for microspheres***

The mucoadherant features of microspheres were determined by in vitro wash-off test described by sativa et al.A 1 x 1 cm section of rat stomach mucosa was firmly attached to a 3 x 1 inch glass slide. Microspheres were uniformly added to the cleaned and moistened tissue sample on this glass slide. The prepared slide was then inserted into a disintegration testing equipment using a platform as directed by the United States Pharmacopoeia (USP).

The apparatus used for the disintegration tests was set up so that the specimen would always move perpendicularly inside a container that was filled with simulated gastric fluid that met USP requirements and had a pH of 1.2. After the first half-hour, and then every hour after that, measurements were taken to find out how many microspheres were still adhered to the sample tissue. This observation persisted for the full 10-hour testing period.

**Preparation, characterization, and evaluation of optimized formulation**

Carefully chosen doses for the formulation were used to create an optimised formulation (MM-TSA).

***Drug release studies***

In vitro release test was conducted with a USP XXIV basket type apparatus containing 900 mL of simulated gastric fluid (pH 1.2) as dissolution medium at 37 ± 0.5°C, which is operated at 100 rpm [18]. A quantity of microspheres equal to 20 milligrammes of glibenclamide was used in the investigation. Five millilitre samples were taken at regular intervals, filtered through a 0.45 micrometre membrane, diluted accordingly, and then subjected to spectrophotometric analysis at a wavelength of 231 nanometers. As soon as test sample collection was completed, a new dissolving medium was added.

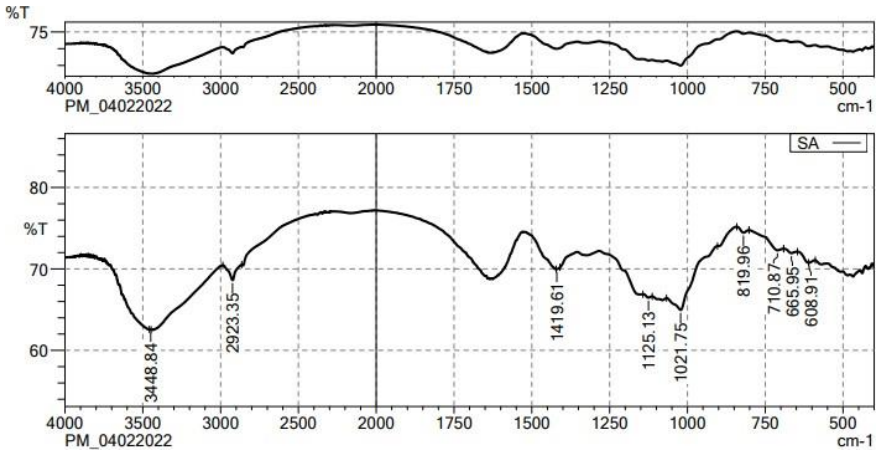
**Biological studies- Cell culture and cell viability**

*Cell cultures and viability test by resazurin assay*

The resazurin (Alamar blue) assay was conducted on Caco-2 cell cultures as reported earlier with similar incubation conditions. Individual sample solutions of thiolated, protected, and unaltered okra gum were prepared, and white MEM was used to create their microparticles at a concentration of 1% m/v. Negative and positive controls were 1% m/v of Triton X-100 and white MEM, respectively [19].

**3. Results and discussion**

Sodium alginate was successfully thiolated and evaluated for various parameters. As a evidence Thiol content of TSA was fund to be 4.37mM. Viscosity was increased to 49.35 mPas The IR spectra of SA and TSA were compared to confirm the thiolation. Figure 1, shown FTIR spectrum of SA and TSA. TSA shown all characteristic peaks of SA in addition to thiol peak (S-H) at 2929.77 $cm^{-1}$. This further confirmed the presence of thiol groups. SEM images also confirmed the changes in the surface morphology of the SA. Initially SA exists in rod like structures later TSA shown spherical particles with reduced particle size.

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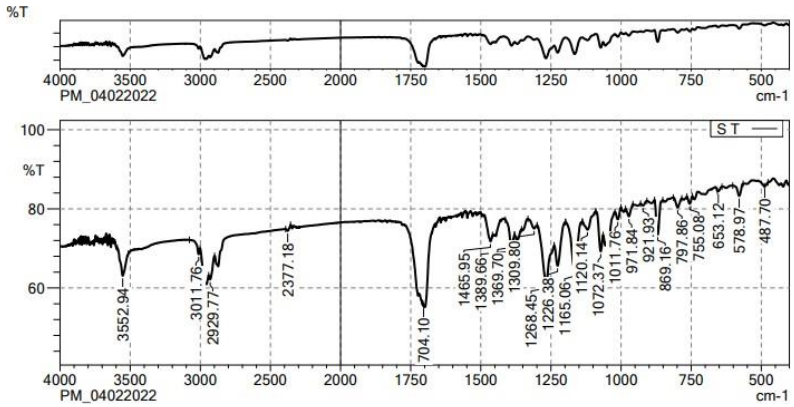


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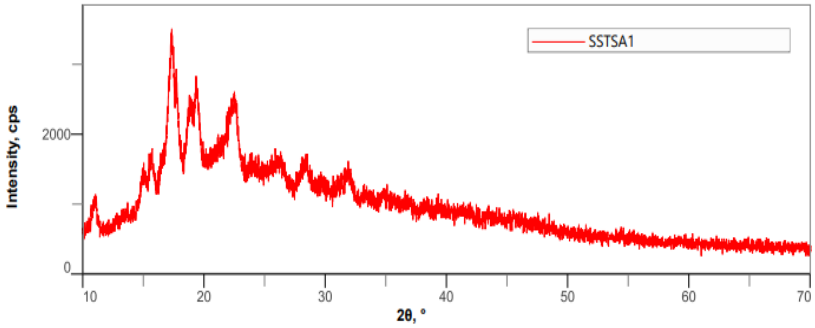
**Figure 1.** FTIR Spectra of SA and TSA

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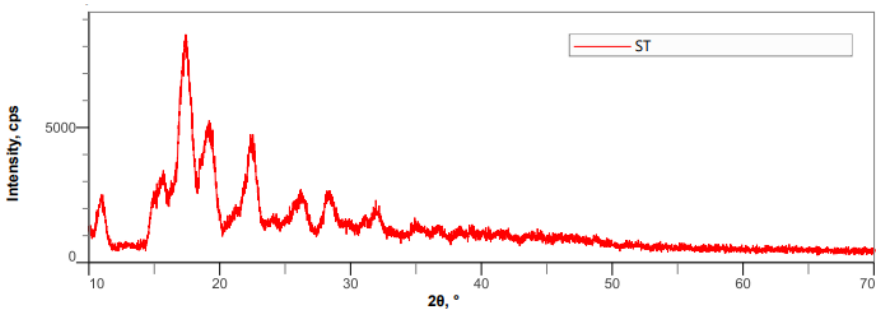



(b)

**Figure 2.** XRD spectra of a)SA and b) TSA

The crystalline structure of the polymer was examined by using a powder Xray diffraction technique. The XRD patterns shows the different peaks of SA and TSA. XRD peaks of SA was observed at 2Ɵ, 10.939,12.95, 15.95, 21.20, 24.17, 28.42, 34.97. The XRD peaks of the TSA was observed at 2Ɵ, 10.98,

15.67,17.38, 26.35, 18.23, 31.93. XRD patterns revealed the rise in intensity after conversion to thiolated polymer [Figure 2].

**Evaluation of Mucoadhesive property**

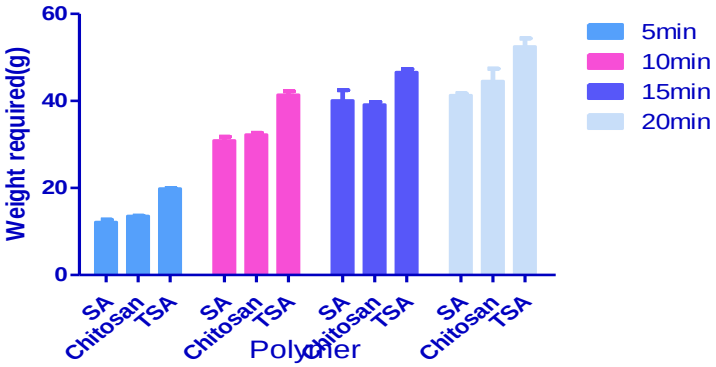



**Figure 3.** Mucoadhesion strength of 1.5% of polymer solutions determined by shear stress method.

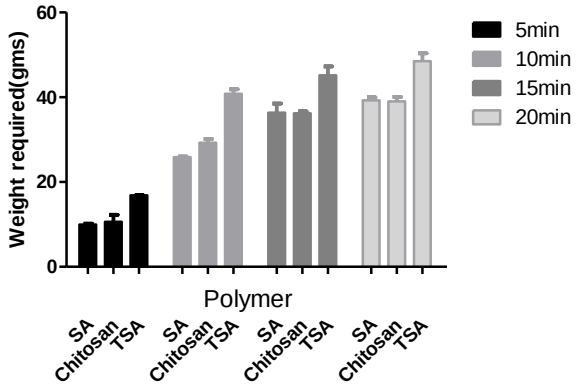



**Figure 4.** Mucoadhesion strength of 0.5% of polymer solutions determined by shear stress method.

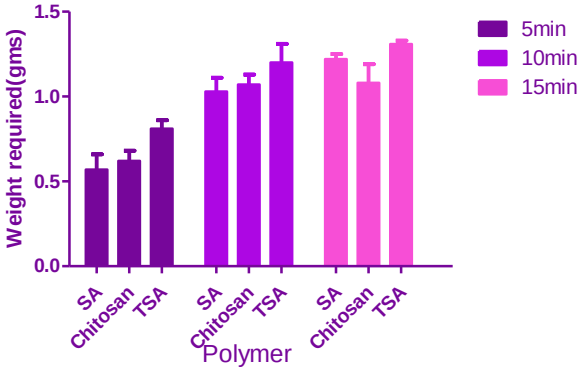



**Figure 5.** Mucoadhesion strength characterized by Wilhelmy's method**.**

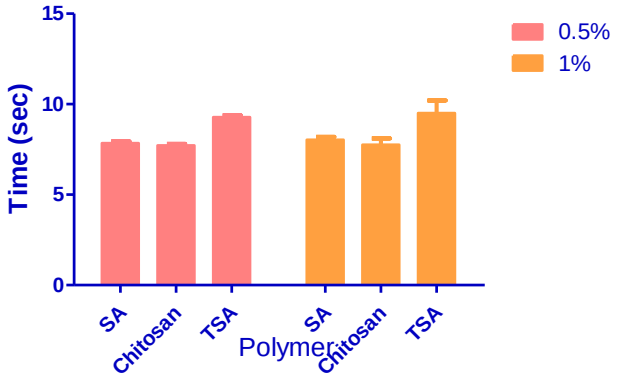



**Figure 6.** Technological characterization of falling sphere analysis at different concentrations.

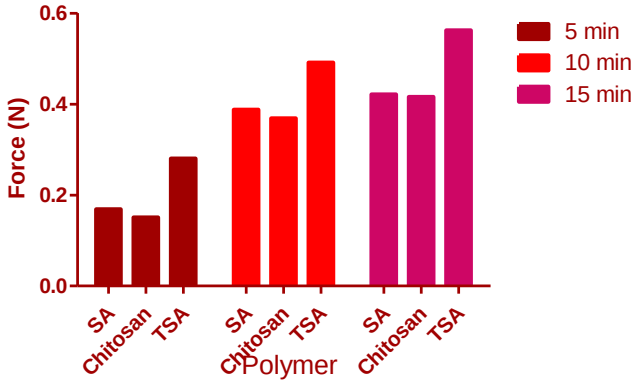



**Figure 7.** Technological characterization of detaching force measurement at different contact times.

All the result shown that mucoadhesive strength of TSA was more than SA and chitosan that confirming the application of thiolation of SA in developing mucoadhesive drug delivery systems.Each polymer sample's viscoelastic characteristics were evaluated rheologically utilising a combination plate-plate rheometer in order to identify any possible correlations between the samples' cytotoxicity. After three hours, the thiomers' dynamic viscosity increased significantly when thioglycolic acid was added to SA, increasing 1.67 times for TSA. After a full day of testing, TSA viscosity unexpectedly increased by more than 3 times. Thiolated polymers may eventually oxidise at normal pH levels, which could result in the creation of intramolecular disulfide linkages. Their viscoelastic properties change with time due to this cross-linking process. This study results with regards to apparent viscosity are shown in Figure 8.

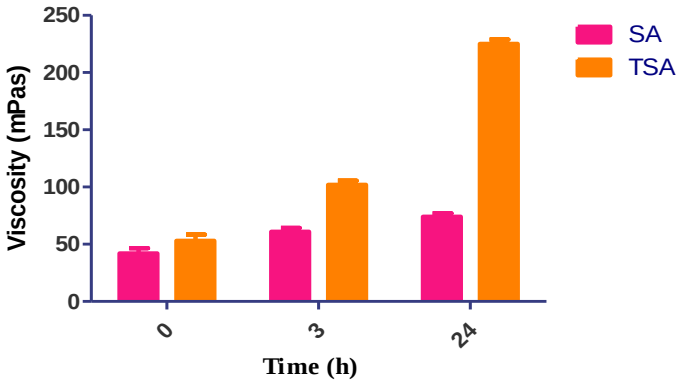



**Figure 8.** Rheological studies of SA and TSA.

**Formulation optimization**

The central composite design of response surface methodology (RSM) was employed to determine the optimal concentration of selected factors and their interactions for achieving the desired encapsulation efficiency (EE) and in vitro mucoadhesion. A total of 13 experimental runs were planned, and the results are presented in Table 3. The EE for all the experimental preparations ranged between 51% and 87%, while mucoadhesion strength varied between 21% and 82%.The obtained results were analyzed for individual responses and the influence of parameters using a quadratic model (fx) and analysis of variance (ANOVA). For both responses, a quadratic high-order polynomial model was chosen, based on the sum of squares (Type I), model summary statistics, and fit summary (see Table 2). This choice was made as the auxiliary terms played a significant role, and the model was not aliased, ensuring a comprehensive representation of the data.Table2. Design summary

| Factor | Name | Units | Type | Minimum | Maximum | Coded Low | Coded High | Mean | Std. Dev. |
|---|---|---|---|---|---|---|---|---|---|
| A | TSA conc | (%) | Numeric | 1.19 | 3.31 | -1 ↔ 1.50 | +1 ↔ 3.00 | 2.25 | 0.6124 |
| B | Stirring Speed | rpm | Numeric | 177.51 | 672.49 | -1 ↔ 250.00 | +1 ↔ 600.00 | 425.00 | 142.89 |

**Table 3.** Projected experimental runs for Box-Behnken design and their observed responses.

| | | Factor 1 | Factor 2 | Response 1 | Response 2 |
|---|---|---|---|---|---|
| Std | Run | A:TSA conc | B:Stirring Speed | EE | In vitro mucoadhesion |
| | | (%) | rpm | % | % |
| 4 | 1 | 3 | 600 | 81 | 82 |
| 5 | 2 | 1.18934 | 425 | 52 | 21 |
| 10 | 3 | 2.25 | 425 | 67 | 69 |
| 3 | 4 | 1.5 | 600 | 52 | 48 |
| 1 | 5 | 1.5 | 250 | 47 | 42 |
| 2 | 6 | 3 | 250 | 71 | 72 |
| 13 | 7 | 2.25 | 425 | 67 | 71 |
| 6 | 8 | 3.31066 | 425 | 87 | 78 |
| 9 | 9 | 2.25 | 425 | 69 | 72 |
| 7 | 10 | 2.25 | 177.513 | 51 | 65 |
| 11 | 11 | 2.25 | 425 | 70 | 70 |
| 12 | 12 | 2.25 | 425 | 67 | 70 |
| 8 | 13 | 2.25 | 672.487 | 68 | 76 |

**Table 4**. Fit Statistics

| Response 1 | | | | | Response 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Std. Dev.** | 1.92 | | **$R^2$** | 0.9847 | **Std. Dev.** | 2.44 | | **$R^2$** | 0.9882 |
| **Mean** | 65.31 | | **Adjusted $R^2$** | 0.9738 | **Mean** | 64.31 | | **Adjusted $R^2$** | 0.9797 |
| **C.V. %** | 2.94 | | **Predicted $R^2$** | 0.9176 | **C.V. %** | 3.80 | | **Predicted $R^2$** | 0.9241 |
| | | | **Adeq Precision** | 30.2872 | | | | **Adeq Precision** | 35.6278 |

The Predicted $R^2$ value of 0.9176 shows reasonable agreement with the Adjusted $R^2$ of 0.9738, with a difference of less than 0.2. Adeq Precision, which measures the signal-to-noise ratio, is greater than 4 (30.2872), indicating a desirable signal level. This model can effectively navigate the design space.To further ensure the model's effectiveness and fitness, fit summary data were applied. The coefficient of variation (CV) is used to assess model repeatability, and in this case, the selected quadratic model displayed a CV of only 2.94%, well below the 10% threshold, confirming its reproducibility.Adequate Precision, which quantifies the signal-to-noise ratio, underscores the model's efficiency in handling the design space. Lack of fit, if present, can render a model ineffective in representing the complete data, making it crucial to assess the coherence of the equations developed by the model for predicting responses.

ANOVA was conducted to investigate the measurable effects of various factors. Polynomial equations were derived through multiple regressions, and the equations obtained from the output of the optimal model are presented in Table 5.

**Table 5.** ANOVA for responses.

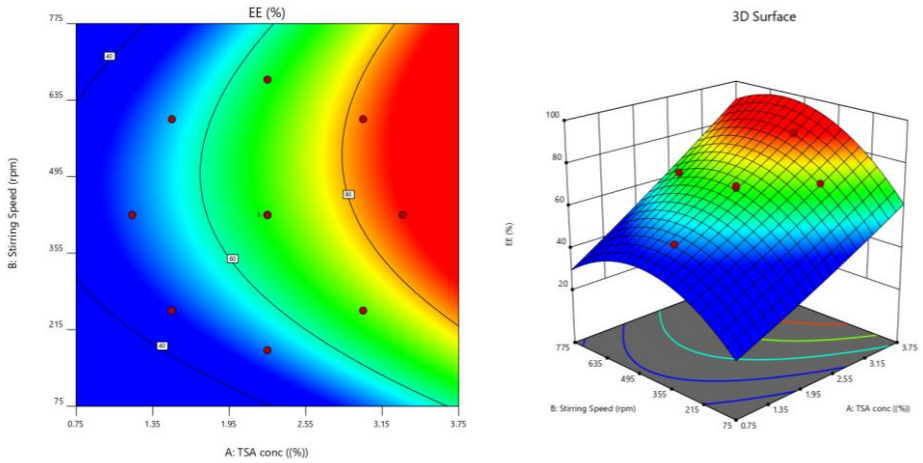
| | Response 1 | | Response 1 | |
|---|---|---|---|---|
| **Source** | **F-value** | **p-value** | **F-value** | **p-value** |
| **Model** | 90.29 | < 0.0001 | 116.97 | < 0.0001 |
| A-TSA conc | 355.23 | < 0.0001 | 438.68 | < 0.0001 |
| B-Stirring Speed | 51.54 | 0.0002 | 20.89 | 0.0026 |
| AB | 1.69 | 0.2347 | 0.6713 | 0.4396 |
| $A^2$ | 0.1838 | 0.6810 | 121.46 | < 0.0001 |
| $B^2$ | 41.35 | 0.0004 | 0.1051 | 0.7553 |

The equation expressed in terms of coded factors serves as a valuable tool for making predictions regarding the response at specific levels of each factor. In this representation, high factor levels are coded as +1, while low levels are coded as -1. This coded equation is particularly useful for assessing the relative influence of the factors by comparing their respective coefficients.

EE = +68.00 +12.81 A +4.88 B +1.25 AB +0.3125 $A^2$ -4.69 $B^2$

In vitro mucoadhesion = +70.40 +18.08 A +3.94 B +1.00 AB -10.20 $A^2$ +0.3000 $B^2$

Additionally, RSM was used to analyze and interpret the impact of individual parameters on the responses. Contour plots, which depict the relationship between selected responses and variables, help visualize the effects of these variables. RSM was employed to assess and interpret the response of independent parameters in relation to the discrete responses obtained.Three-dimensional surface graphs are essential for illustrating the interaction and main effects. Contour plots were utilized to predict the obtained responses, aiding in a comprehensive understanding of the relationships between variables and responses.

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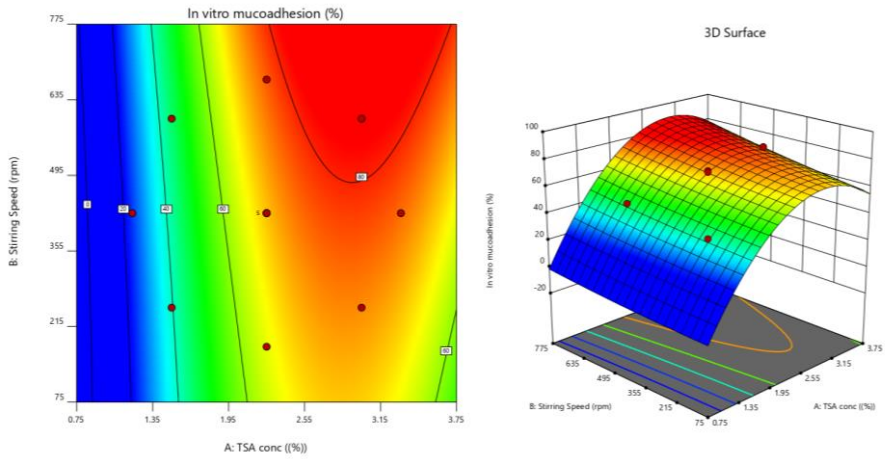


(b)

**Figure 9.** Contour and response surface graphs for a) response 1 and response 2.

The Global Desirability Function (D) was utilized to standardize the model's order as determined by statistical analysis. In the desirability function plot, the optimal levels of independent variables were associated with a maximum D value of 0.950 for both responses. Consequently, following this configuration leads to an encapsulation efficiency (EE) of 83.10% and in vitro mucoadhesion of 82.00%.Furthermore, the contour plot, which reveals the relationships between chosen responses and variables, helps assess variable effects. Response Surface Methodology (RSM) was employed to estimate and interpret the responses of independent parameters in relation to the discrete responses obtained. Three-dimensional surface graphs were instrumental in illustrating interactivity and main effects, while contour plots were employed to predict the obtained responses.Using the optimized concentrations, an optimized formulation (MM-TSA) was prepared and evaluated to validate the study design. As required, the relative error was found to be less than 5%, confirming the accuracy of the design. The same formulation was used to assess the remaining parameters.

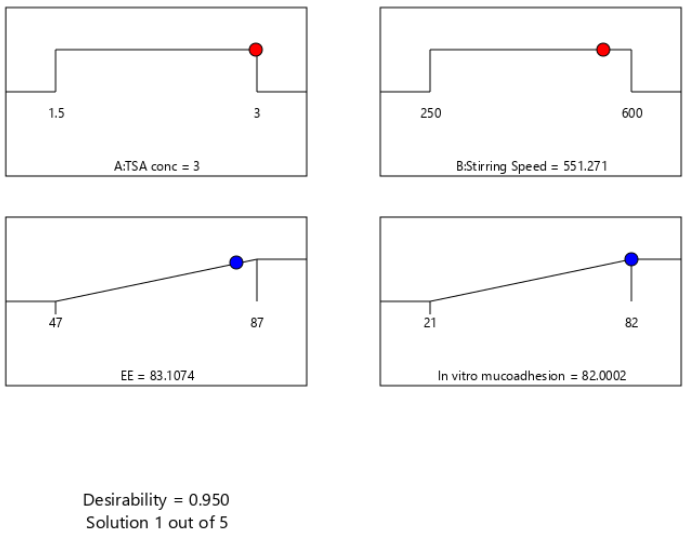


**Figure 10**. Desirability plot or optimization result.

**In vitro dissolution study**

MM-TSA formulation shown considerable sustained drug release till the end of 24 h. Drug release results were further calculated for drug release kinetics. Thiolation renders information of 3D gel organization and inter-/intrachain disulfide bonds (this could enhance the cross-linkage and cohesive nature of the matrix), therefore improving the passage for the media diffusion. Drug release kinetics of MM-TSA follows controlled release with anomalous (non-Fickian) diffusion mechanism (slop value of Korsmeyer–Peppas model- n = 0.6979).

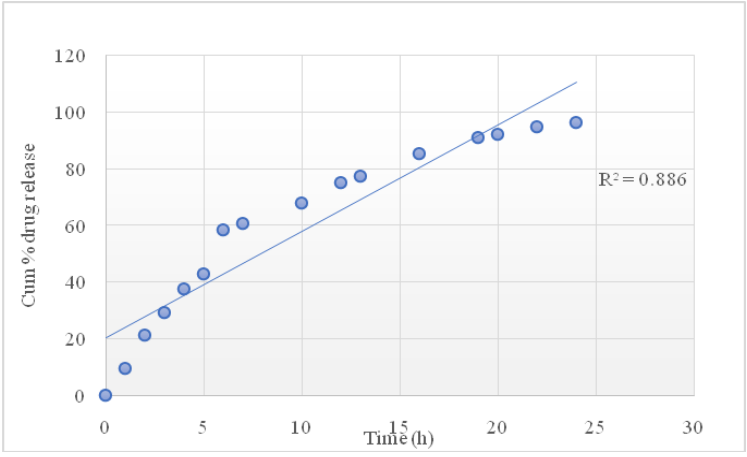


**Figure 11. (A)** Zero order plot for MM-TSA

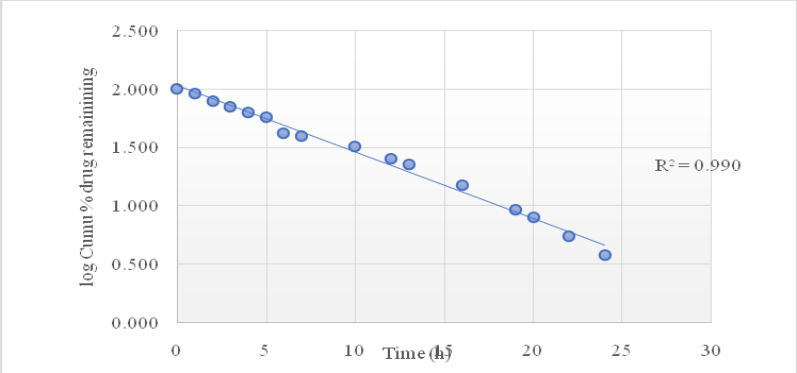


**Figure 11.** (B) First order plot for MM-TSA

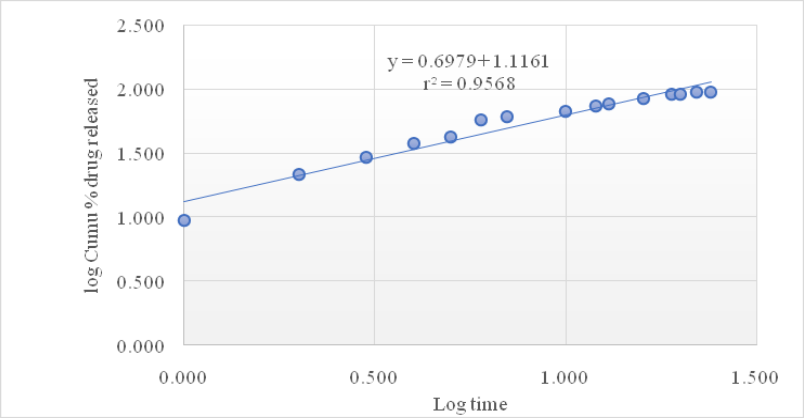


**Figure 11.** (c) Korsmeyer and Peppas plot for MM-TSA

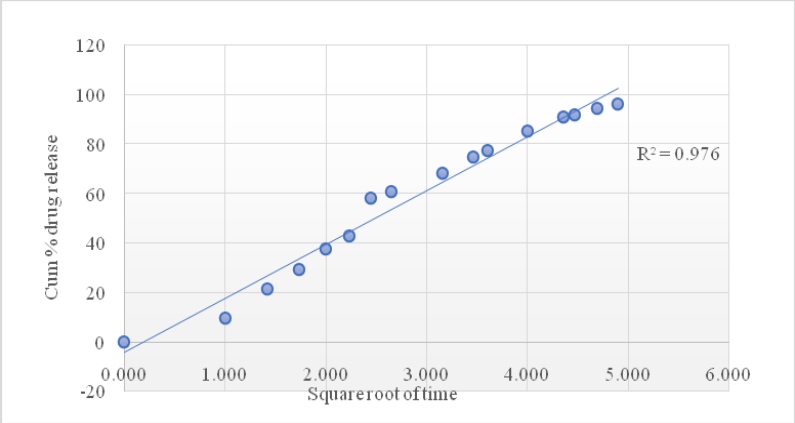


**Figure 11.** (d) Higuchi plot for MM-TSA

***Stability studies***

There were no changes in the physical appearance of the micropsheres during the storage conditions of the study course. The dissolution profile of the test samples was compared by computing similarity and dissimilarity factors using the standardized formulation as a reference to ensure the drug release. All the stored samples exhibited a good similarity profile (>90) with respect to the reference formulation [Table 6].

**Table 6.** Stability studies for O-EH-UF.

| TEST | INITIAL | 25 °C±2 °C+60%±5% RH | | 40 °C ±2 °C+75% ±5% RH | |
|---|---|---|---|---|---|
| | | 3 M | 6 M | 3 M | 6 M |
| Mucoadhesion | 82.5 | 82.1 | 81.7 | 81.8 | 81.5 |
| *f* 2 | -- | 87.61 | 88.75 | 85.61 | 78.83 |

**Conclusion:**

Thiomers, with the potential to form intermolecular and intramolecular disulfide bonds, play a significant role in enhancing mucoadhesion strength, improving swelling, and sustaining drug release. Thiolated polymers have been observed to exhibit enhanced mucoadhesion potential. In this study, thiolated sodium alginate (TSA) was synthesized and characterized for its rheological properties and the quantification of thiol/sulfide groups. The preparation of etoricoxib microspheres was optimized using a central composite design. According to the desirability approach, an optimal formulation comprising 3% TSA and a stirring speed of 551.271 rpm met the criteria for achieving an encapsulation efficiency of 83.10% and 82% mucoadhesion retention.The optimized formulation was further evaluated for drug release and cell viability. Cell viability studies indicated that all thiolated formulations were non-cytotoxic, as cell viability remained high. The MM-TSA formulation demonstrated significant sustained drug release over 24 hours, with drug release kinetics following a controlled release with anomalous (non-Fickian) diffusion mechanism. This research explores innovative drug delivery systems, particularly thiolated sodium alginate-based mucoadhesive microspheres, which offer promising solutions for targeted and time-specific drug administration.

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