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TRIGONELLA FOENUM-GRAECUM L. SEED MUCILAGE-BASE MUCOADHESIVE MICROSPHERES OF DICLOFENAC SODIUM

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Keywords:

Microspheres, *Trigonella foenum-graecum* L. seed mucilage, Mucoadhesion, Diclofenac sodium

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ABSTRACT: The study was aimed to discover the properties of *Trigonella foenum-graecum* L. seed mucilage (TFGSM) in the formulation of mucoadhesive microspheres of diclofenac sodium to prolong the residence time at the site of absorption. Diclofenac sodium microspheres were formulated by ion gelation technique. Different polymer ratios of TFGSM and sodium alginate were used to formulate eight formulations (F1 to F8) of TFGSM-based mucoadhesive microspheres of diclofenac sodium and characterized by determining their percentage yield, drug entrapment efficiency, swelling index, mucoadhesive and drug release. The drug entrapment efficiency of all eight formulations was within the range of 78 to 98% with the sustained *in-vitro* release of over 8 h. The *in-vitro* drug release of these microspheres followed controlled release (zero-order). The microspheres possessed good swelling properties and mucoadhesive properties. Diclofenac sodium microspheres were observed to adhere strongly with gastric mucosa with approximately 14 h of prolonged stay expecting improved bioavailability and reduced dosing frequency and subsequently improving patient's compliance. Diclofenac sodium microspheres can be effectively used for sustained drug release and prolonged residence at the site of absorption.

INTRODUCTION: Arthritis is an incurable condition that cannot be cured, especially in chronic cases, by general medication practices but treatments to manage the symptoms and slow the progression are available. Arthritis refers to conditions that involve pain and inflammation of the joints. Patients with arthritis seek treatment, mainly due to the uncomfortable pain that restricts their daily routines. Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used in the management of arthritis-related pain. They are effective and available as prescription and non-prescription products.

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Non-prescription NSAIDs are often used without taking into account the contraindications as they are easily available [1]. Concerns of the usage of NSAIDs are associated with gastrointestinal (GI) side effects and increased cardiovascular risk [2].

Diclofenac sodium is an NSAID having anti-inflammatory, analgesic, and antipyretic actions. Pharmacokinetically, it rapidly metabolizes due to its relatively short half-life of 1-2 h and has an absolute bioavailability of 55% when administered orally due to first pass metabolism effect [3, 4]. Patients require multiple dosing regimens resulting in reduced compliance and poor therapeutic effect significantly. Concerns of the long term usage of diclofenac sodium, like most NSAIDs, is associated with GI problems such as peptic ulcers and GI bleeding along with risks of cardiovascular adverse effects [5]. These concerns of GI side effects have generated more researches to overcome the side effect and improve the therapeutic effects of

diclofenac sodium, leading to the development of various conventional oral formulations of diclofenac sodium. Microsphere drug delivery is a multi-particulate system, has been researched to improved absorption and reduces GI irritation that uniformly spreads at the site of absorption, which is usually formulated using polymers. However, polymeric microspheres have short residence time at the site of absorption leading to the development of mucoadhesive microspheres by incorporating mucoadhesive polymers that allow the microspheres to adhere to the mucous tissue and thus, prolong the residence time [6].

Trigonella foenum-graecum L. seed mucilage (TFGSM) has been investigated as a mucoadhesive polymer. It is originally isolated from *Trigonella foenum-gracum* L. seeds which contain a significant amount of mucilage. It is pharmaceutically investigated as binding agent [7], disintegrating agent [8], and mucoadhesive gelling agent [9]. However, only a few investigations used *Trigonella foenum-graecum* L. seed mucilage (TFGSM) as a mucoadhesive excipient in the formulation of the mucoadhesive polymer-based microsphere, and none of the studies used diclofenac sodium as the active ingredient in the development of TFGSM-based mucoadhesive microspheres. In the development of TFGSM-base mucoadhesive microsphere, various studies aim to improve the mucoadhesive property to extend the residence time at the site of absorption as well as to achieve drug encapsulation efficiency and drug release that is within the desired range.

The formulation of mucoadhesive polymer-based microspheres using ionotropic gelation techniques is well established [10]. By using this ionotropic gelation technique allows the polymers to be physically cross-linked to form microspheres and to avoid the utilization of expensive and toxic reagents [11]. This technique requires counterions to form the cross-linking.

In previous studies, TFGSM demonstrates promising mucoadhesive properties and is easily available and inexpensive. It offers a new alternative of plant-based mucoadhesive polymer to be used in the formulation of mucoadhesive microspheres. To best of knowledge; no studies have formulated TFGSM-based mucoadhesive microspheres containing diclofenac sodium. It has the potential to prolong the residence time at the absorption site, thereby, eliminating frequent dosing and improve patient compliance resulting in improve therapeutic effects. It is beneficial, especially to patients that require long term use of diclofenac sodium such as patients with arthritis.

MATERIALS AND METHODS:

Materials: The diclofenac sodium salt was purchased from Sigma Aldrich chemicals Ltd., sodium alginate, and all other chemicals were purchased from Sigma Aldrich chemicals Ltd. All the solvents and chemicals used in this study were of analytical-reagent grade. Deionized double distilled water was used throughout the study for any preparation and formulations.

Methods: *Trigonella foenum-graecum* L. seeds (200 g) were soaked in 1.5 l of distilled water for 24 h and boiled using water bath until the preparation of slurry is obtained. The slurry was allowed to cool down and kept in the refrigerator overnight to settle out undissolved materials. The clear upper solution was gradually poured and concentrated at 60 ºC using a water bath to one-third of its original volume.

The solution was allowed to cool down and transferred into three times the volume of acetone with continuous stirring. The precipitate was washed repeatedly with acetone and dried at room temperature for 24 h. The isolated material was passed through sieve number 80 and stored in desiccators until further use [15].

Evaluation of TFGSM:

Solubility: Solubility of TFGSM was performed by dissolving in distilled water and organic solvents such as chloroform and methanol [12-13].

Swelling Index: TFGSM 1 g was transferred into a 25 ml glass stoppered measuring cylinder, and 25 ml of distilled water was added and shaken vigorously every 10 min for 1 h and will be allowed to stand for 24 h. The volume occupied by the TFGSM was measured. The process was repeated three times and the swelling index was calculated from the mean of three readings [14, 16.]

Loss on Drying: Loss on drying was determined by weighing 1 g of TFGSM and heated at 105 ºC

until a constant weight is achieved using a hot air oven [17].

The percentage of moisture loss on drying was calculated using the following formula:

Loss on drying (%) = Weight of water in sample × 100 / Weight of dry sample

pH: TFGSM 5 g with 20 ml of distilled water and stirred for 5 min. the pH of the resulting TFGSM mixture was determined using a calibrated digital pH meter (Hanna instruments pH 211 microprocessor-based bench pH meter, USA) [17].

Bulk Density: Bulk density was determined by adding pre-weighed amounts of TFGSM into a graduated cylinder, and the volume was recorded. The powders were introduced to tapping in a bulk density apparatus until a constant volume is an achieved [18]. The tapped density was determined as the ratio of the sample weight to the final sample volume [19].

Percentage Yield: The yield of the TFGSM was calculated using the formula below:

Yield (%) = Amount of TFGSM achieved (g) × 100 / Amount of TFG seed (g)

Preparation of TFGSM-Based Mucoadhesive Microspheres of Diclofenac Sodium: Sodium alginate and TFGSM was weighed and separately dissolved in purified water and mixed to form a polymer dispersion mixture. Diclofenac sodium was added to the polymer dispersion mixture and mixed thoroughly. The resulting polymer-drug dispersion mixture was added drop-wise via a syringe with a needle (No. 23) into calcium chloride (10% w/v) solution. The added droplet was retained in the calcium chloride solution for 15 min to complete the reaction and to produce spherical microspheres.

TABLE 1: FORMULATIONS OF TFGSM-BASED MUCO-ADHESIVE MICROSPHERES OF DICLOFENAC SODIUM

Batches	Diclofenac sodium (g)	TFGSM (g)	Sodium alginate (g)
F1	1	0.5	0.5
F2	1	1	0.5
F3	1	1.5	0.5
F4	1	2	0.5
F5	1	0.5	1
F6	1	1	1
F7	1	1.5	1
F8	1	2	1

Microsphere was collected by decantation and washed with water and dried overnight at room temperature [20]. Formulations of TFGSM-based mucoadhesive microspheres of diclofenac sodium are shown in **Table 1**.

Evaluation of TFGSM-Based Microspheres of Diclofenac Sodium:

Percentage Yield: The percentage yield of the formulated microspheres was determined using the equation below:

Yield (%) = Amount of microspheres prepared × 100 / Amount of drug + polymer taken

Determination of DEE: 100 mg of microspheres was crushed and transferred in a 250 ml volumetric flask, and the volume was made up to 250 ml using phosphate buffer, pH 7.4 and kept for 24 h with occasionally shaking at 37 ± 0.5 °C. After the specified time, the mixture was stirred at 500 rpm for 20 min using magnetic stirrer. The polymer remaining after the disintegration of microspheres was removed by filtering through Whatman filter paper (No. 40) [15]. The drug content in the filtrate was determined using a UV spectrophotometer at 276 nm against an appropriate blank. The DEE (%) of these prepared microspheres was calculated by the following formula:

DEE (%) = Actual drug content in microspheres × 100 / Theoretical drug content in microspheres

***In-vitro* Drug Release Studies:** The dissolution rate of microspheres was tested using dissolution apparatus, rotating basket method with two different pH values, pH 1.2, and pH 7.4. The basket was covered with 100 mesh nylon cloth to prevent the escape of the microspheres. The dissolution rates will be measured at 37 ± 1 °C, 50 rpm speed. A weighed quantity of microspheres containing diclofenac sodium (100 mg) was added to 900 ml of 0.1 N HCl, pH 1.2. The test was carried out for 2 h and then continued in phosphate buffer (pH 7.4) for next 8 h. 5 ml of aliquots were collected at regular time intervals, and the same amount of fresh dissolution medium was replaced into dissolution vessel to maintain the sink condition throughout the experiment. The collect aliquots were filtered and diluted to determine the absorbance using UV spectrophotometer at 276 nm against appropriate blank [15].

Swelling Study: The swelling behavior of the TFGSM-based mucoadhesive microspheres of diclofenac sodium was evaluated by swelling index test [15]. Swelling index test of TFGSM-based mucoadhesive microspheres of diclofenac sodium was performed in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) aqueous mediums. 100 mg of microspheres were placed in the beaker of dissolution apparatus containing 500 ml of respective media. The experiment was carried out at 37 ± 1 °C under 50 rpm paddle speed. The swelled microspheres were removed at a predetermined time interval and weighed after drying the surface by using tissue paper.

The swelling index was determined using the following formula:

Swelling index (%) = Weight after swelling – Dry weight × 100 / Dry weight of beads

Ex-vivo* Mucoadhesion Testing*: The mucoadhesivity of TFGSM-based mucoadhesive microspheres of diclofenac sodium was evaluated by the *ex-vivo* wash-off method. A 1-cm by a 1-cm piece of rat stomach mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. Exactly 50 microspheres were placed onto a wet tissue specimen, and the prepared slide was hung onto the groove of the disintegration test apparatus. The tissue specimen was given a regularly up and down movement in a beaker containing 900 ml of 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) separately at 37 ± 0.5 °C. At the end of the time interval, the number of microspheres that remained attached to the stomach mucosa was recorded [21].

***In-vitro* Drug Release Kinetics and Mechanism:** To determine the drug release kinetic and mechanism for the formulated TFGSM-based mucoadhesive microspheres of diclofenac sodium, the *in-vitro* data was evaluated to find a suitable mathematical model to fit the *in-vitro* release behavior. The following mathematic models were evaluated to determine the drug release per unit time: zero order and first order. Higuchi and Korsmeyer-Peppas model was used to evaluate the mechanism of drug release [15].

Zero Order:

$$Q = kt + Q_0$$

Where Q represents the drug release amount in time t andQ_0 is the start value of Q; k is the rate constant.

First-Order Model:

$$Q = Q_0 e^{k.t}$$

Where Q represents the drug released amount in time t andQ_0 is the start value of Q; k is the rate constant.

Hugachi Model:

$$Q = kt^{0.5}$$

Where Q represents the drug released amount in time t and k is the rate constant.

Korsmeyer-Peppas Model:

$$Q = kt^n$$

Where Q represents the drug releases amount in time t, k is the rate constant, and n is the release exponent, indicative of drug release mechanism.

These models were compared by calculating the squared correlation coefficient (R^2)[22, 23]. Following, the Korsmeyer-Peppas model was used in the *in-vitro* release pattern evaluation of the formulations to distinguish between completing release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport) and case-II transport (relaxation-controlled release). When n is ≤ 0.43, it is Fickian release. The n value between 0.43 and 0.85 is defined as non-Fickian release. When n value is ≥0.85, it is case-II transport [24].

Fourier Transform-Infrared (FTIR) Spectroscopy: Samples were powdered and analyzed using a Fourier transform infrared (FTIR) spectroscopy (Perkin Elmer Spectrum two, USA). A small amount of sample powders was placed in the sample area. Spectral scanning was taken in wavelength between 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION: The solubility of diclofenac sodium in distilled water at room temperature was 2.86 µg/ml. The melting point was determined using an open capillary method. The average melting point of diclofenac sodium was 288.66 °C, meeting the specification as stated in

British Pharmacopoeia that the range of diclofenac sodium should fall in between 288-290 °C. The standard curve of diclofenac sodium was determined in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.4) at 276 nm. The graph was plotted with concentration as x-axis and absorbance on the y-axis. The plotted graphed followed the Beer-Lambert's law in the concentration of 10 – 60 µg/mL with a regression correlation (R^2) of 0.97502 in 0.1 N HCl and 0.98727 in phosphate buffer that is approximately close to 1 indicating good linearity in this range of concentration [25].

The yield of TFGSM isolated from *Trigonella foenum-graecum* L. seeds obtained was less (3.17% w/w) when compared to that of previous isolation performed by other researchers having a higher yield (17.36% w/w) [15]. Various tests were performed to evaluate the physicochemical properties and to understand the properties of the TFGSM powder obtained from the isolation of *Trigonella foenum-graecum* L. seed. Results of physicochemical characteristics of TFGSM powder are shown in **Table 2**.

TABLE 2: PHYSICOCHEMICAL CHARACTERISTICS OF TFGSM POWDER

Tests	Results
Organoleptic Characteristics	
Colour	Light brown powder
Odor	Odorless
Solubility	
Distilled water	Swells in contact with water and forms tacky mass.
Methanol	Insoluble
Chloroform	Insoluble
Swelling index	
Method I	30 ml
Method II	735
Loss on drying	0.46 g
pH	6.23
Bulk density	0.60 g/ml
Tap density	0.69 g/ml
Yield	3.17 %

Evaluation of TFGSM-Based Mucoadhesive Microspheres of Diclofenac Sodium: The microspheres were prepared by ionotropic gelation technique using TFGSM and sodium alginate as the mucoadhesive agent and calcium chloride as the cross-linker. The polymeric solution of TFGSM, sodium alginate, and diclofenac sodium were added drop-wised into the calcium chloride solution using a syringe (No. 23) forming the microspheres. Sodium alginate is a negatively charged polymer that allows the reaction with positively charged ions present in the calcium chloride solution resulting in the formation of microsphere [23]. The microspheres general appearance was spherical with rough surfaces and light brown due to the original pigmentation color of the TFGSM.

It was found that in most formulations when the polymer ratio of the formulation increases, the percentage yield also increases. However, low percentage yield can be seen even with high polymer ratio; this might be occurred due to blockage of the needle, wastage of the drug-polymer solution and loss during transferring and washing. The percentage yield ranged from 87.40 to 97.80%. The DEE (%) of F1 to F8 range of 77.97 to 98.05%, as shown in **Table 3**. It was found that the DEE (%) was influenced by the increasing polymer ratio of sodium alginate and TFGSM. As the viscosity of the polymeric solution increased, the DEE (%) decreased. This might be due to the increasing TFGSM resulting in a viscous polymeric solution which might have prevented the drug release to the calcium chloride solution. From all eight formulations, F6 was found to have the highest DEE (%) of 98.05.

TABLE 3: DRUG ENCAPSULATION EFFICIENCY OF F1 TO F8

Formulation	Drug Encapsulation Efficiency (%)
F1	96.87
F2	95.69
F3	94.51
F4	92.15
F5	95.69
F6	98.05
F7	81.51
F8	77.97

The *in-vitro* dissolution studies of all eight formulations (F1 to F8) of TFGSM-based mucoadhesive microspheres of diclofenac sodium using a dissolution tester USP (Electrolab, TDT-08L), basket method in 900 ml of pH 1.2 for 2 hrs and pH 7.4 for 8 h at 37 °C and 50 rmp. At each time interval, 10 ml of each formulation was taken, and UV absorbance was recorded. The formulations exhibits a percentage cumulative drug release (CDR, %) in the range of 88.50% to 97.70% and were found that in formulations with decreasing ratio of TFGSM was higher. It was found that diclofenac sodium release from these

microspheres in pH 1.2 was slow, less than 15.90% after 2 h. This event might be due to shrinkage of alginate at acidic pH as alginate is known to be pH sensitive [23, 24]. In comparison, the drug release was observed to be more rapid in phosphate buffer, due to the higher swelling rate of these microspheres. F6 showed the highest CDR (%) of 98.50%. The *in-vitro* drug release of all formulations F1 to F8 is shown in **Fig. 1**.

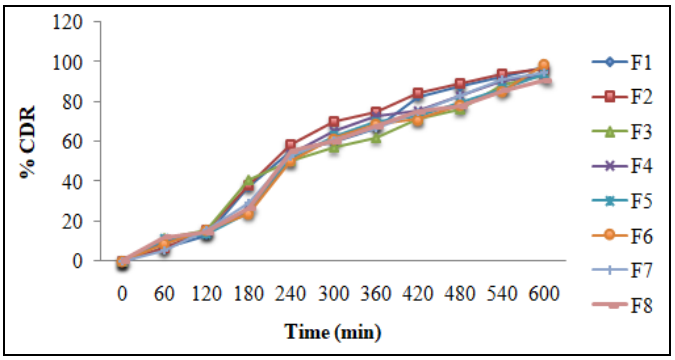

FIG. 1: *IN VITRO* DRUG RELEASE OF F1 TO F8

The swelling pattern of F1 to F8 ionotropically TFGSM-based mucoadhesive microspheres of diclofenac sodium was evaluated in 0.1 N HCl and phosphate buffer. The swelling patterns of these microspheres in both medium were shown in **Fig. 2** and **3**. It was observed that as the polymer concentration increases, the microspheres swells more. Initially, the extent of swelling of these TFGSM-based mucoadhesive microspheres of diclofenac sodium was lower in the acidic medium compared with that of in phosphate buffer. This resulted due to shrinkage of alginate in acidic pH [23]. Maximum swelling of the microspheres was observed at 2-3 h in phosphate buffer and followed by erosion and dissolution.

It was reported that phosphate ions present in the phosphate buffer could behave as calcium sequestrates, allowing further swelling of calcium alginate microspheres. This swelling pattern of TFGSM-based mucoadhesive microspheres of diclofenac sodium in phosphate buffer resulted by the exchange of ions between calcium ions present in phosphate buffer with the influence of calcium sequestrate phosphate ions. This phenomenon might result in the disaggregation of the TFGSM and alginate matrix structure resulting in matrix erosion and dissolution of the swollen microspheres [26, 27]. These indicate that these TFGSM-based mucoadhesive microspheres of diclofenac sodium may show slight swelling in the stomach as they subsequently move to the upper intestine, where the diclofenac sodium is to be absorbed, and these microspheres continue to swell more.

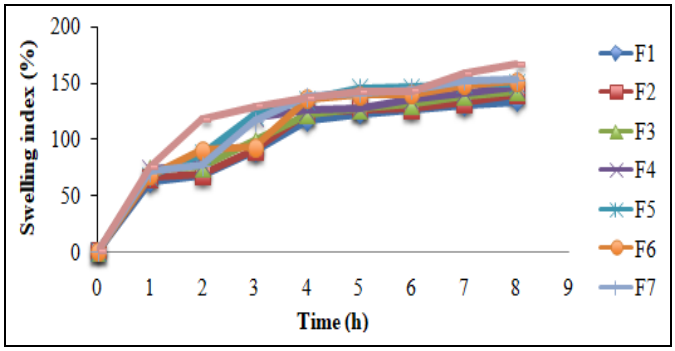

FIG. 2: SWELLING BEHAVIOUR IN 0.1 N HCl (pH 1.2)

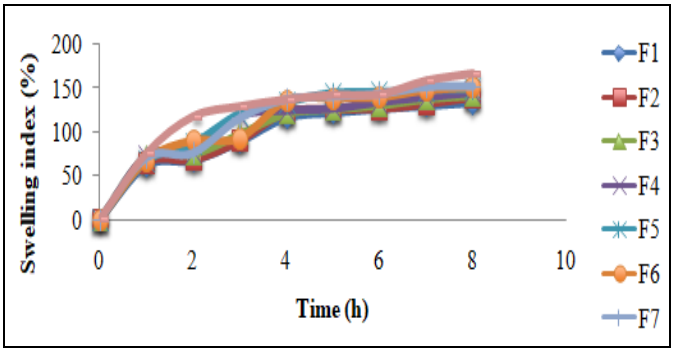

FIG. 3: SWELLING BEHAVIOUR IN PHOSPHATE BUFFER

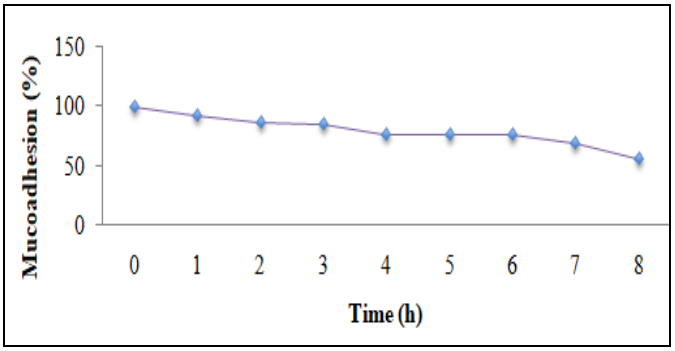

FIG. 4: RESULT OF *EX-VIVO* WASH-OFF TEST FOR (F6) IN PHOSPHATE BUFFER

The *ex-vivo* wash-off test was performed using rat stomach mucosa for evaluating the mucoadhesive property of TFGSM-based mucoadhesive microspheres of diclofenac sodium for F6 was performed at stomach pH for 8 h using disintegration apparatus. The percentage of microspheres remained adhered to the rat stomach mucosal tissue was 56% over 8 h, shown in **Fig. 4**.

The decreasing trend of the mucoadhesion of TFGSM-based mucoadhesive microspheres of

diclofenac sodium in phosphate buffer might be occurred due to the erosion of calcium ion. Therefore, the results of the wash-off test indicated that TFGSM-based mucoadhesive microspheres of diclofenac sodium possessed good mucoadhesive.

TFGSM-based mucoadhesive microspheres of diclofenac sodium F6 was evaluated mathematically for its drug release kinetics model like zero order, first order, Higguchi, and Korsmeyer-Peppas models. The R^2 of these models were determined and compared. The R^2 of TFGSM-based mucoadhesive microspheres of diclofenac sodium F6 were compared, it was found to follow zero-order model ($R^2 = 0.966$) as the best-fit model throughout 8 h amongst others.

This was also observed to be closest to the Higuchi model ($R^2 = 0.964$). Finally, the best fitting of the zero-order model indicates that the drug release from F6 microspheres followed a controlled-release pattern. The value of diffusional exponent (n) determined from the Korsmeyer-Peppas model (n = 0.188), indicating the drug release from these microspheres followed Fickian mechanism. Fickian diffusion refers to the solute transport process in which the polymer relaxation time is much greater than the characteristic solvent diffusion time [28].

The FTIR spectra of diclofenac sodium, TFGSM, sodium alginate, and TFGSM-sodium alginate microspheres containing diclofenac sodium are shown in **Fig. 5** to **8**. The FTIR spectrum of diclofenac sodium showed the bands around 611.70, 748.06, 1452.30 and 1603.84 cm^{-1}, which are due to the bending of =C-H and stretching of C=C. In FTIR spectrum of TFGSM showed absorption characteristic peaks of ether linkage C-O at 1015.97 and aromatic stretching of C-H at 3286.14 cm^{-1}. The FTIR spectrum of sodium alginate showed peaks at 1024.75, 1407.82 and 1594.77, indicating the presence of an ether linkage C-O, -C-H bending alkenes and C=C aromatic stretching. Lastly, the FTIR spectrum for TFGSM-sodium alginate microspheres containing diclofenac sodium showed several characteristics of peaks of diclofenac sodium, sodium alginate, and TFGSM were present and showed no shifting of these peaks, suggesting there were no interactions between drug and excipient used (sodium alginate and TFGSM).

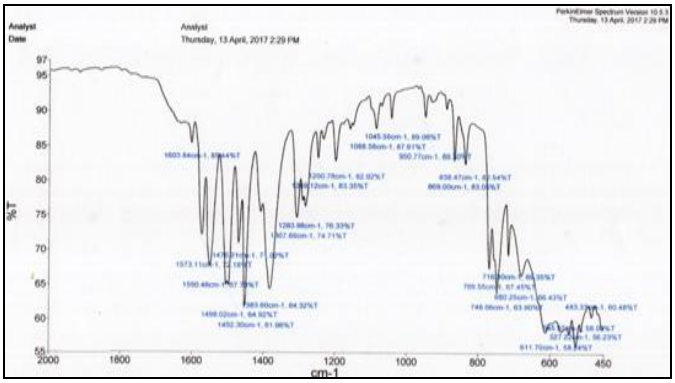

FIG. 5: FTIR SPECTRUM OF DICLOFENAC SODIUM

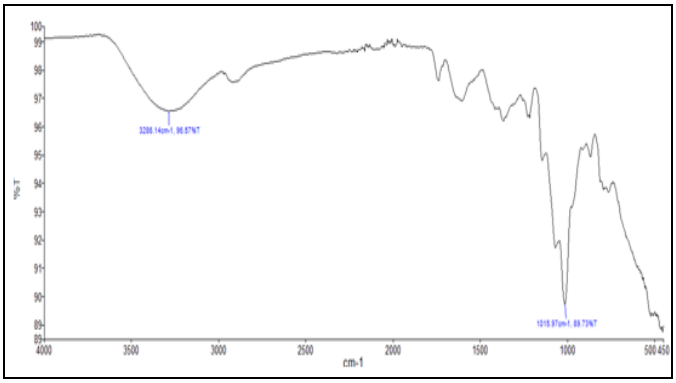

FIG. 6: FTIR SPECTRUM OF TFGSM

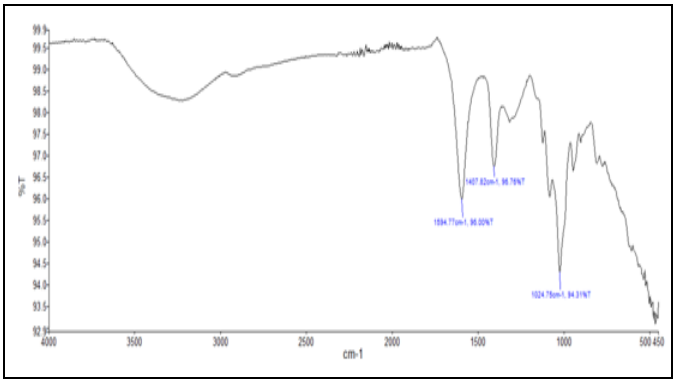

FIG. 7: FTIR SPECTRUM OF SODIUM ALGINATE

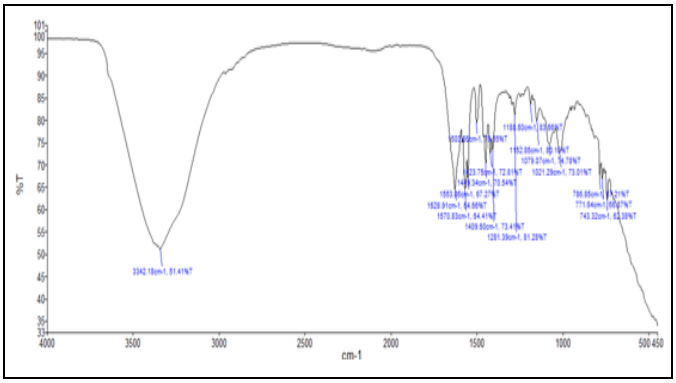

FIG. 8: FTIR SPECTRUM OF TFGSM-BASED MICROSPHERES OF DICLOFENAC SODIUM

CONCLUSION: TFGSM-based mucoadhesive microsphere of diclofenac sodium by ionotropic gelation techniques were successfully formulated and evaluated. The study shows that the TFGSM-based microspheres formulated were able to prolong gastric residence time by swelling slowly in the stomach and adhering to the stomach mucosa which then will subsequently move to the intestine and swells more allowing the release of the drug. Thus, TFGSM serves as a potential mucoadhesive excipient in the formulation of the controlled-release mucoadhesive microsphere.

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CONFLICT OF INTEREST: Nil

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