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Formulation and Evaluation of Gastroretentive, Sustained Release Floating Beads of Aceclofenac by Non-Effervescent Method

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KEYWORDS
Floating Beads, Oil Emulsification, Ionic gelation, Sustained release, Gastro-retentive, Sodium alginate, Gelatin.

ABSTRACT:

Introduction: Bioavailability enhancement for a drug with a short biological half-life and low water solubility is a great challenge for a researcher. Various drug molecules (like metformin HCl, baclofen, etc.), whose major site of intake is the part of the digestive system or the proximal part of the small intestine.

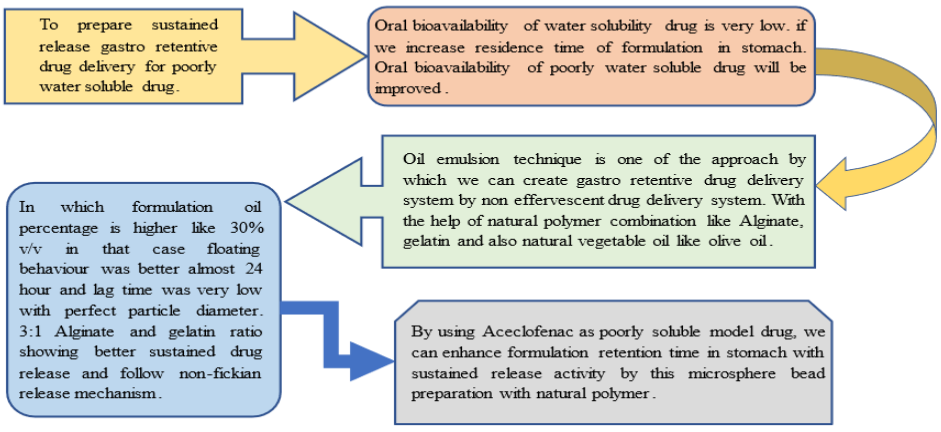
Objectives: The drug Aceclofenac has a relatively low dissolution rate, brief half-life and is readily bypassed by the stomach without effective absorption. To overcome this problem we prepare sustained release gastro-retentive floating non effervescent type multi-particulate system.

Methods: In the present study Gastro-retentive non effervescent type floating bead is prepared using Aceclofenac as a model drug and by using the oil emulsification and ionic gelation process to get better buoyancy of microsphere bead with short lag time for floating and good drug loading capacity.

Results: From the characterization study of optimum floating bead, it is observed that floating time almost 24 hr. with very short floating lag time within 15 seconds, more than 90% drug entrapment efficiency and 12 hours sustained release of drug is observed. The formulation F5 showed high entrapment efficiency (90.12%) as well as more sustained effects.

Conclusion: The present study demonstrated a successful preparation of floating beads of Aceclofenac by emulsion gelation method. These results suggest that developed gastro retentive floating beads can improve the bioavailability of Aceclofenac, reduce its dosing frequency, and enhance its patient compliance.

Graphical Abstract of Aceclofenacloaded floating microsphere bead by emulsification gelation method forgastro retentivesustained release drug delivery system:



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1. Introduction:

Oral formulations have taken the lead from the various dosage forms explored so far for general consumption. Because of rapid stomach emptying time and other factors, the standard oral administration methods often exhibit low bioavailability. [1,2] To address this issue, controlled release medication delivery systems are among the numerous unique pharmaceutical solutions that have emerged as a result of recent technological advancements. One such example is the gastro-retentive treatment modality (GRDDS), where the coupling of a delayed medicine release with a stomach retention time has significantly boosted patient compliance. The interest in this delivery technology has been sparked by several inherent shortcomings of the traditional oral medication administration systems. Various drug molecules (like metformin HCl, baclofen, etc.), whose major site of intake is the part of the digestive system or the proximal part of the small intestine or who have a problem with digestion in the lateral part of the gastrointestinal tract, have a bioavailability issue as a result of rapid gastric acid secretion related to conventional mucosal treatments.[3-5] Longer lengths of time in the stomach can boost the absorption of medications that are less absorbed in the alkaline condition of the intestine. Many drugs are vulnerable to disintegration in the colon, including captopril, metronidazole, ranitidine HCl, etc. Since they often leave the systemic circulation, medications with short half-lives require repeated dosages to have the intended therapeutic effect. A sustained-release oral formulation with improved stomach retention properties, on the other hand, can get around these restrictions by slowly releasing the medication into the stomach while still keeping an efficient long-term medication retention in the systemic circulation[6]. By eliminating the Hepatitis pylori bacteria from the mucous membrane tissue of the stomach, GRDDS has shown that it may successfully treat localised esophagitis, stomach and intestinal ulcers, and duodenal ulcers.[2,5,7,8,9]

It is also feasible to target site-specific medication release in the upper gastrointestinal tract (GIT) for local or systemic impacts using a method known as gastro-retentive dosage forms. Multiple gastro-retentive drug administration strategies have been created and improved over the past several years, including high density (sinking) mechanisms that are retained in the stomach's bottom[4], low density (floating) mechanisms that cause buoyancy in gastrointestinal fluid[5, 6,10] bio adhesion processes that cause bio adhesion to the abdominal mucosa[7], and unfold able, elongated, or soluble structures that prevent disposal of the pharmaceutical formulations through the intestines. [7]

However, multiple unit dose formulations are required when medication excipients or drug physicochemical interaction is possible in a single-unit formulation. These are also known to move through the gastrointestinal tract more uniformly than single-unit dosing approaches. Granules, beads, pellets or mini tablets are the subunits, and the dosage forms are typically built on subunits. Mostly solid capsules or tablets made with gelatine which degenerate instantly. [22]

Bioavailability can be good for multi particle systems as they have a higher likelihood of attaining entire drug release than monolithic single-unit SR dose formulations.

Owing to the slower release base, a single unit system could not be capable of delivering the maintenance dosage. Low medication solubility and/or a preoccupation window where absorption occurs in an insufficient area of the gastrointestinal zone would be detrimental.[11]

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) that has a low water solubility. The medicine Aceclofenac has a relatively low dissolution rate and is readily bypassed by the stomach without effective absorption. It is known that prolonged therapy produces side effects including gas, stomach irritability, ulcers and abdominal discomfort. Due to its brief half-life, a daily dosage of 200 mg split into two doses is advised (4 hours). A sustained-release gastro retentive Aceclofenac dose is essential for long-term therapy to decrease dosing frequency and unpleasant side effects. [12,13,14,15]

Recent research focusing on long-acting dosage forms has as one of its key goals the utilization of natural polymers as drug carriers. Among these, sodium alginate has received much research and application due to its potential to control drug release, biodegradability, and lack of toxicity.[21]

However, sodium alginate has certain drawbacks, including uncontrollable disintegration, instability at lower pH levels, and bigger pore sizes that affect drug release. Alginate and other biopolymers, such gelatin, may so work together to extend the life of the finished product. Alginate and gelatin combine to generate a more solid structure that can limit medication release and provide longer-lasting effects thanks to hydrogen bonds and ionic interactions. [16-18,13]

2. Objectives

Aceclofenac was chosen as the model medication in the current investigation, and I used the emulsion gelation

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procedure to create gastro retentive Aceclofenac floating beads. The use of oil-entrapped alginate-gelatin floating beads as a gastro-retentive prolonged Aceclofenac release dosage form to boost oral bioavailability and decrease dose frequencies may thus be advantageous. [19,20]

3. Methods

Materials

Sodium alginate was purchased from Loba Chemie Pvt. Ltd., India (F-624-625 & G1-135, Industrial Area, Khushkhera, (Near Bhiwadi), Tapukara, Distt. -Alwar, Rajasthan-301707, India). Gelatin & Magnesium stearate were purchased from HiMedia Laboratories Pvt.Ltd., 35/B, Subhas Sarobar Park, Phool Bagan, Beleghata, Kolkata, West Bengal 700010. Olive oil of lova was purchased locally. Tween 80, Sodium chloride, Calcium chloride & Potassium dihydrogen phosohate was procured from Merck Specialities Private Limited, Mumbai – 400018). Hydrochloric acid, Aceclofenac and Methanol were procured from Merck Life Science Private Limited, Mumbai 400079.

Methodology

Aceclofenac loaded gelatin-alginate beads preparation:

Aceclofenac-containing gelatin-alginate beads by oil emulsification method were created using the ionotropic emulsion-gelation process. In short, in100 ml of demineralized water, the exact amount of polymers in a ratio (sodium alginate and gelatin) were dissolved by magnetic stirring with heat. After that the prepared solution keep at room temperature for 30min to cool down. To form a white emulsion, in the prepared polymer solution, olive oil, MS (Magnesium stearate) and tween 20 (10%, V/V), was combined with constant stirring. In the emulsion drug was added and the mixture was then agitated for 15 to 20 minutes at 5000 rpm using a homogenizer. All the compositions maintained a drug-polymer ratio of 1:3. The resultant emulsion was added drop wise to the $CaCl_2$ solution with mild agitation by magnetic stirrer at room temperature using 21G needle. The synthesized gel beads were left in the mixture for 15 minutes before being removed by filtering and being rinsed three times with distilled water. The beads were dried at room temperature and kept in the desiccator until needed. Table 1 shows the compositions of different batches.

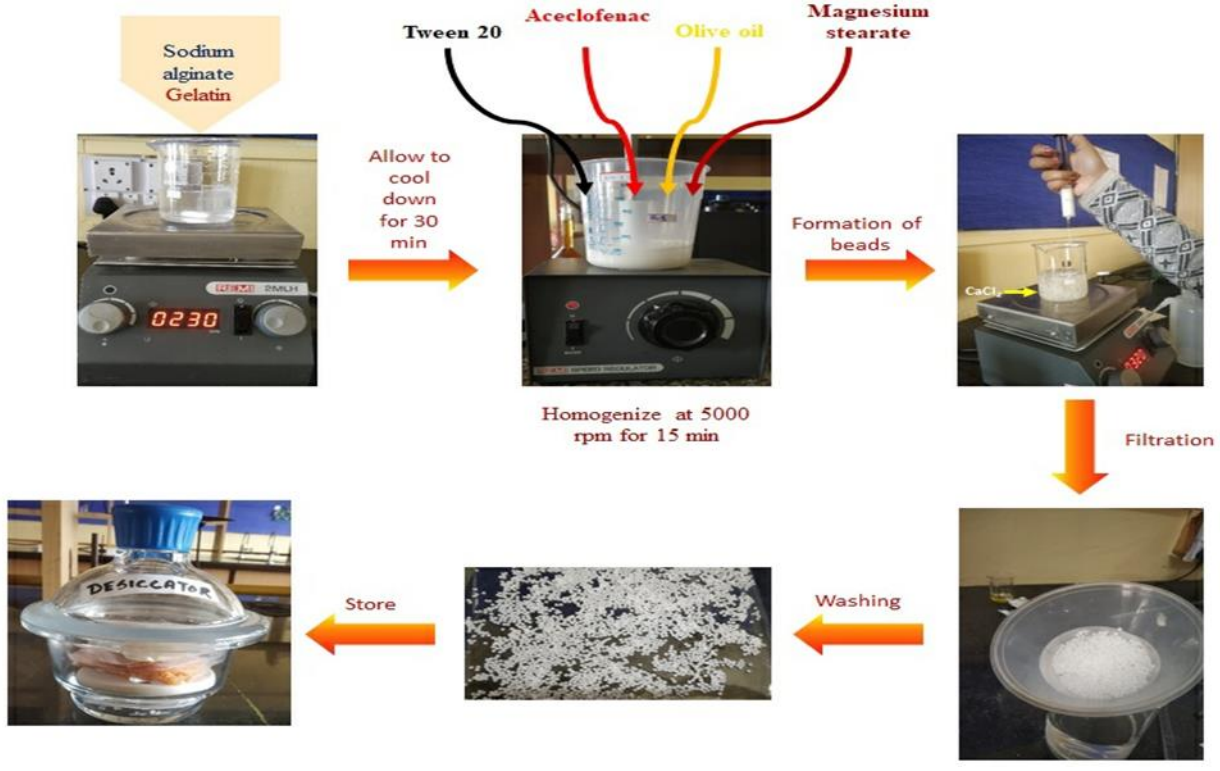

Fig 1: Schematic diagram of Aceclofenac-containing gelatin-alginate encapsulated beads by oil emulsification method.

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Formula code	Sodium alginate %(W/V): Gelatin (W/V)	Drug (gm)	Olive oil %(V/V)	Tween %(V/V)	MS %(W/V)	$CaCL_2$ %(W/V)
F1	1:3	1	30	10	0.6	10
F2	1:2	1	30	10	0.6	10
F3	1:1	1	30	10	0.6	10
F4	2:1	1	30	10	0.6	10
F5	3:1	1	30	10	0.6	10
F6	3:1	1	20	10	0.6	10
F7	3:1	1	5	10	0.6	10
F8	3:1	1	30	-	0.6	10
F9	3:0	1	-	-	-	10
F10	3:1	-	30	10	0.6	10

Table 1: The composition of different formulations

4. Results

Physicochemical characterization of prepared beads:

Fourier transform infrared Study:

To detect the probable drug-excipient interaction and any changes in functional groups FTIR spectroscopy was performed. Place the sample on top of the crystal's surface and then enclosed with a gripper plate. This process is performed for drug, gelatin-alginate beads without drug and with drug. Samples were scanned with a wave number range of 4,000-400 cm1 in a Bruker Alpha II FTIR spectroscope.[24,25,16,17,26,27,13]

Surface morphology study: The microbeads, which underwent a 20-second platinum coating process at 1.1V under an argon atmosphere using the ion Auto Fine Coater JFC-1600 (JOEL, Japan), were affixed to metal stubs. Subsequently, double micrographs were captured under vaccum. .[16,17,26,27]

Particle size analysis:

An optical microscope has been used to analyse the particle size and distribution. To perform this particle size analysis 100 alginate beads were collected and placed under a calibrated optical microscope to assess particle size. Then each formulation were assessed in triplicate.[28,19]

In vitro buoyancy evaluation

Dissolution apparatus type- II was used to measure the buoyancy of beads (VEEGO). In 900 ml of simulated gastric fluid (pH 1.2) at 37°C with 50 RPM rotation, 50 beads were placed. The floating lag time and total floating were recorded.[29,30,31,32]

Drug entrapment efficiency study of gelatin-alginate beads

From each sample, 100 mg of manufactured beads that were accurately weighed were taken out and crushed in a pestle and mortar. After crushing, the granules were dispersed and soaked in 500 ml of pH 6.8 phosphate buffer for 24 hours at 37.5°C. Filtration was done by Whatman filter paper to remove the undissolved particle and the absorbance (max) of the filtrate was calculated by Shimadzu spectrophotometer (UV-1800) at 273.50 nm.[33,34,35] The drug entrapment capacity of microparticles was calculated using the formula below:

$$DEE\ \% = \frac{\text{Actual drug content in microparticles}}{\text{Theoritical drug content in microparticles}} \times 100$$

In vitro drug release study from gelatin-alginate beads:

Using a dissolution apparatus type I (VEEGO) basket type, the in vitro release of Aceclofenac from gelatin-alginate beads was assessed. In 900 ml of pH 1.2 HCl buffer, maintained at 37°C, weighed amount of beads containing 100 mg of drug was taken for in-vitro dissolution study.[36,37,38,39,40] Throughout the study, 5 ml of sample was withdrawn at specific intervals and were filtered and further diluted for spectroscopic analysis to determine the drug release on a Shimadzu UV-1800 UV-VIS spectrophotometer at 272.6 nm.[41,42,43,44,45] Calculations were done about the percent drug release at various time intervals. Cumulative Percent release vs time was plotted, and different kinetic models were

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studied to understand the release patterns of the drug from the formulation. [46,47,48,49,50]

Dosage forms kinetics of dissolution

To analyze the release kinetics, data from in vitro drug distribution studies were shown in a variety of kinetic parameters: The accumulated amount of medicine delivered over time is plotted in Equation 1's zero order. First phase as a logarithmic time-dependent accumulated percentage of medicine remaining (Equation 2), Equation 3 of the Higuchi model plots the cumulative amount of medication released against the square root of time and
Equation 4 by Korsmeyer plots the logarithmic amount of sustained release over time.

5. Discussion

Fourier transform infrared analysis:

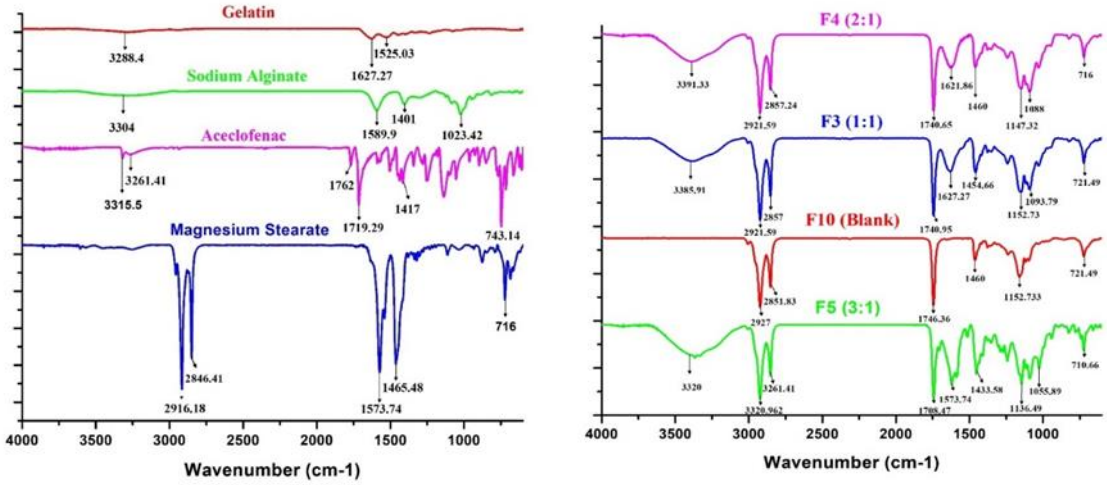

Fig 2. FT-IR spectrum of excipient and drug (A), FT-IR spectrum of Different formulation (B)

Here drug-excipient interaction was determined using FTIR spectroscopy. Fig.a shows the FTIR spectra of each of the polymers (alginate, gelatin), excipient and drug. For asymmetric and symmetric C=O stretching vibrations of COO- ions, sodium alginate's FTIR spectra exhibited typical main peaks at 1589.9 cm-1 and 1401 cm-1, respectively. In addition, the OH stretching mode led to the observation of a large range at 3304 cm-1. Gelatin's FTIR spectra exhibited distinctive bands for N-H stretching at 3288.4 cm-1, C=O stretching at 1627.27 cm-1, N-H bending vibration at 1525.03 cm-1, and C-N stretching vibration at 1525.03 cm-1. Magnesium stearate's FTIR spectra exhibited peaks for the 2asymmetric and symmetric carboxylate (COO-) asymmetric stretching at 1573.74 cm-1 and 1465.48 cm-1, correspondingly. Although the peaks at 2916.18 cm-1 and 2846.41 cm-1 are caused by the C-H stretching mode. The distinctive bands in the FTIR spectra of pure aceclofenac were at 3315.5 cm-1 (N-H stretching), 3261.41 cm-1 (O-H stretching), 1719.29 cm-1 (C=O stretching), 1762 cm-1 (C=O stretching of carboxylic acid), and 743.14 cm-1 (1,2 di-substituted C-Cl stretching). In fig.b which shows the FTIR spectra of formulation. In the spectra of formulation between 1400 – 1700 cm-1 characteristic peaks of polymer and excipient have been found. A characteristic peak of aceclofenac at 3320 cm-1 in the formulation has been found which is absent clearly in the blank formulation which indicate drug is incorporated into the developed beads. Thus, this result show that polymer -polymer and drug-polymer interaction is not occurred.

Scanning electron microscopy: SEM images of formulation F5 shows spherical structure and more even surface edges with low porosity due to high sodium alginate concentration but SEM images of F1 shows more porous and uneven surfaces due to low proportions of sodium alginate. Blank beads show a more uniform shape and smoother surfaces than F5 which is loaded with drug, so due to entrapment of drug, surface of bead become slightly uneven and small amount of pores are created. Figure 3 showing SEM images of F1, F5 and blank formulation.

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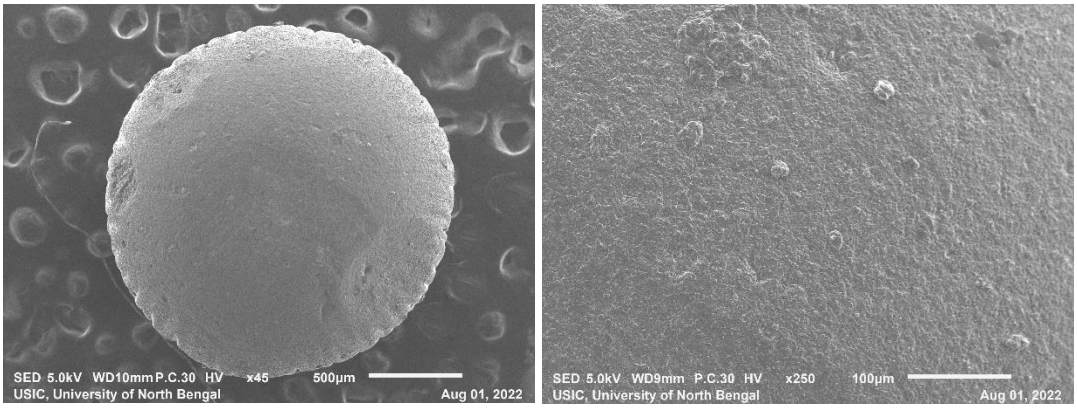
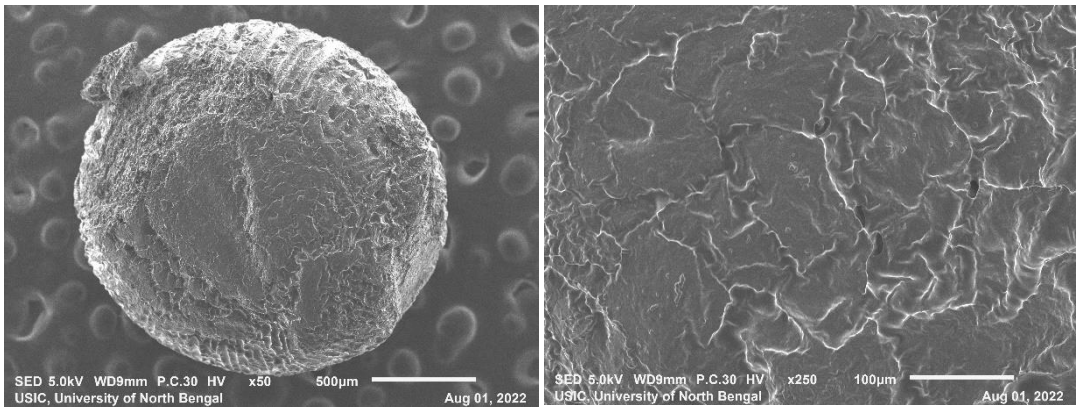
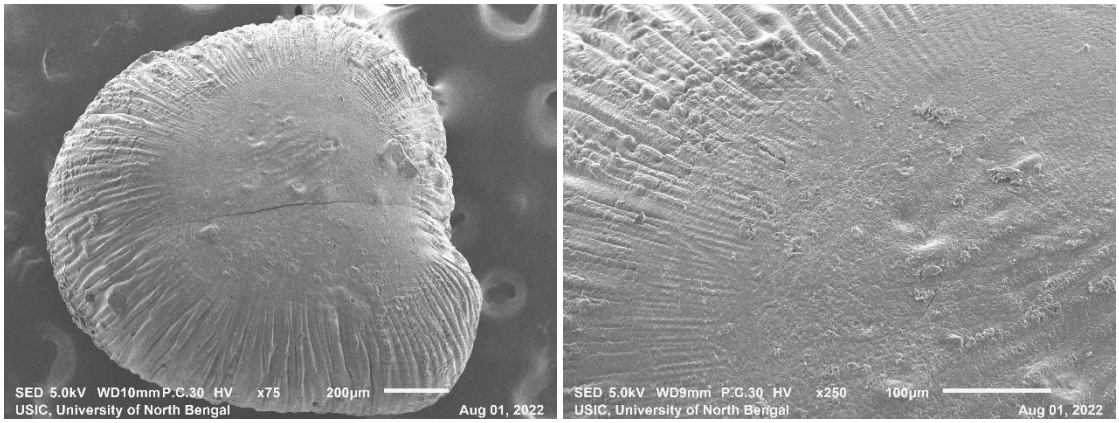


(a)



(b)



(c)

Fig 3. SEM image of optimized batch of Blank (a), F1 (b) and F5 (c)

Particle size analysis: Evey formulation's distribution of particle sizes was tightly constrained to a small size range. The beads' average diameter varied from 1.32 to 1.80 mm. The average mean diameter of the beads rose as sodium alginate content rises. High amounts of alginate can enhance the emulsion's viscosity, which might encourage the creation of beads with bigger particle diameters.

Buoyancy: The varying batches all revealed the same lag time. The mean density of the beads was shown to be inversely correlated with the lag time. It is clear that regardless of the amount of oil in the compositions, every bead composition floated within 15 minutes of being put into the acidic medium and stayed buoyant throughout the investigation. Floating is mostly caused by oil that is trapped in the bead (i.e., oil acts as floating aid). This theory is supported by the finding that non-oily beads failed to float for 24 hours whereas oily beads did.[7] To develop a homogeneous emulsion and many, microscopic pockets in the alginate matrix for higher buoyancy, olive oil is used as the dispersed phase. Additionally, during dissolution, medication was

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released from the bead matrix, and swelling lowers density, which also makes floating easier. Regardless of the amount of polymer present in the various batches, it had been found that formulations (F3, F4, F5) containing a higher proportion of oil had shorter lag times and, as a result, enabled the beads to float relatively more quickly than compositions (F6) containing a smaller share of oil. Moreover, adding MS might make the beads less dense and give them more buoyancy. During the entire research (more than 24 hours), every bead stayed buoyant.

Drug entrapment efficiency of oil entrapped gelatin-alginate beads: The substantial drug entrapment effectiveness of aceclofenac-containing gelatin alginate beads entrapped in olive oil may be due to the oil and magnesium stearate inserts. Aceclofenac, a hydrophobic medication, may partition more effectively into the oil phase after olive oil is added. Moreover, the oil and MS form a solid barrier that prevents drug transport to the external medium during processing, increasing the beads' ability to load drugs. The polymer mix ratio has a significant impact on the entrapment efficiency. Raising the sodium alginate content enhanced drug trapping, which was caused by a reduction in drug loss from the very viscous polymer gel. In contrast, the higher concentration of gelatin decreases drug entrapment efficiency. This is due to the weakening structure of the high concentration gelatin beads which might have larger pore size. The formulation F5 shows high drug entrapment efficiency of 90.12%.

Formula code	Mean Particle diameter (mm)	Floating lag time (minutes)	Floating ability	Floating duration (hours)	Entrapment efficiency %	Oil leakage
F1	1.64	-	no	24	36.42	Not seen
F2	1.69	-	no	24	40.21	Not seen
F3	1.71	11.23	float	24	72.56	Not seen
F4	1.75	5.36	float	24	83.91	Not seen
F5	1.80	4.41	float	24	90.12	Not seen
F6	1.79	13.20	float	24	88.25	Not seen
F7	1.79	-	no	-	-	Not seen
F8	1.78		float		-	seen
F9	1.32	-	no	-	84..6	NA
F10	1.72	4.12	float	24	-	Not seen

Table 2: Physicochemical properties of oil-entrapment beads

In vitro medication release research: For F1 through F5 and for F9 in pH 1.2 for 12 hours, the in vitro drug discharge investigation was conducted. The in vitro drug release from the formulations F4 and F5 was sustained over a 12-hour period. (Fig.4). This is due to the ratio of alginate and gelatin mixtures which control the polymer swelling and give the sustained effects in acidic pH 1.2. The formulation F1 and F2 showed burst release within 3 to 4 hrs. This may be because these beads inflate more quickly in acidic pH 1.2.

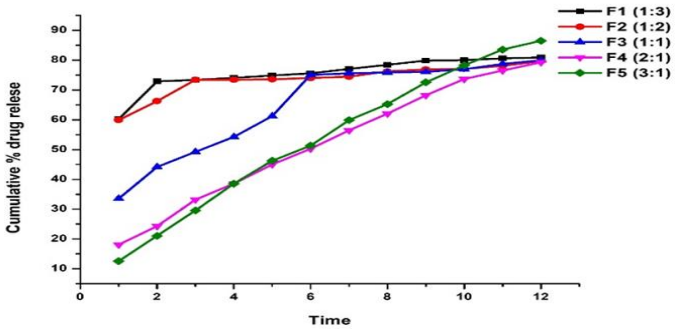

Fig4. *In- vitro* drug release study

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Table 3 shows the findings of curve fitting into several scientific methods (zero order, first order, Higuchi, and Korsmeyer-Peppas). When the appropriate correlation analysis (R2) was revealed, it was noticed that the Higuchi model provided the greatest match for the drug release kinetics. It was observed that formulations F4, F5, and F9 follow a non-Fickian diffusion mechanism based on release exponent data (Table 3). The formulation F1, F2 follow Fickian diffusion.

Sample No	First order (R^2)	Zero order (R^2)	Korsmeyer-Peppas (R^2)	Release exponent (n)	Higuchi (R^2)
F1	0.8338	0.7333	0.9419	0.09	0.823
F2	0.8197	0.7481	0.9294	0.10	0.844
F3	0.894	0.8506	0.9687	0.34	0.9246
F4	0.9889	0.9903	0.9951	0.76	0.9918
F5	0.975	0.9903	0.9989	0.77	0.9938
F9	0.9176	0.8112	0.9989	0.77	0.9085

Table 3: Results of the in vitro drug's curve fitting discharge profile of Aceclofenac-containing alginate-gelatin beads in simulated gastric fluid (pH 1.2)

6. Conclusion

The present study demonstrated a successful preparation of floating beads of Aceclofenac by emulsion gelation method. It has been observed that appropriate techniques are essential to achieving high entrapment effectiveness and prolonged drug delivery from alginate beads. Aceclofenac alginate beads may be effectively formed using the emulsion gelation process. The amount of sodium alginate in the beads had an impact on the Aceclofenac releases from them. By raising the sodium alginate concentration, dosage form was more consistently effective and entrapment effectiveness enhanced. The formulation F5 showed high entrapment efficiency (90.12%) as well as more sustained effects. And also, by the addition of magnesium stearate, olive oil in the solution can alter the drug encapsulation and release characteristic. These developed floating beads exhibited excellent floating ability >24 hrs with a minimum floating lag time. The floating ability of beads depends on the amount of oil used. It has been found that proper ratio of alginate and gelatin can control the drug release with more sustained effects with no burst release. In low pH the disadvantage of alginate, which is instability, can be resolved by proper blending of gelatin. These results suggest that developed gastro retentive floating beads can improve the bioavailability of Aceclofenac, reduce its dosing frequency, and enhance its patient compliance.

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Author Contribution DS: conceptualization, experimental supervision; SS: writing review, and editing; SP, SP: writing original draft; GN: writing, reviewing, and editing. All authors have read and approved this article for publication.

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