

Formulation, Optimization and Characterization of Floating-Mucoadhesive Microspheres of *Terminalia chebula* Extract

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Abstract: The rationale of the study is to develop and evaluate floating-mucoadhesive microspheres encapsulating *Terminalia chebula* extract. Microspheres were formulated using ethyl cellulose to provide buoyancy and control release rate, Eudragits100 as a mucoadhesive polymer, and polyvinyl alcohol as an emulsifier. Microspheres were characterized by scanning electron microscopy and evaluated utilizing micrometric studies, including bulk density, tapped density, particle size, entrapment efficiency, *in vitro* buoyancy, and percentage yield. In-vitro mucoadhesive and drug release studies were carried out for sustained release evaluation. The resultant formulations yield buoyancy greater than 75 %, with a maximum of 89.3%. The formulation containing drug: polymer, 1:1, showed the best results, with 100.08± 0.95 particle size, 88.68 % percentage yield, 87.45% entrapment efficiency, and 98.4% in-vitro release within 7 hours. Mucoadhesive-floating microspheres can effectively treat gastric mucosa and gastric ulcers with a sustained-release effect.

Keywords: Ulcers, Mucoadhesive microspheres, Floating microspheres, Buoyancy, Sustained release.

1. Introduction

The term "gastric ulcer" describes a profound mucosal tissue defect of the stomach mucosa triggered by gastric acid and pepsin, which pierce the muscularis mucosa [1]. A peptic ulcer (PU) illness occurs when environmental factors harm the digestive tract, destroying the stomach mucosa and submucosal involvement. Peptic ulcer disease is thought to affect 5–10% of people in the general population [2]. Major problems such as bleeding, perforation, nausea, vomiting, or obstruction of the gastric outlet are frequently associated with them. In terms of symptoms, health-related quality-of-life degradation, and expenses, this places a significant burden [3-4]. *H. pylori* infection, alcohol and tobacco usage, non-steroidal anti-inflammatory drug (NSAID) use, and Zollinger-Ellison syndrome are risk factors for peptic ulcer development [5]. The primary option for treating stomach ulcers is pharmaceutical therapy administered orally. Anti-ulcer therapies, including proton pump inhibitors, histamine blockers, antacids, and others, cause several side effects, such as headache, diarrhea, thrombocytopenia, cramping in the abdomen, and many more. As a result, there is an urgent need for anti-ulcer drugs that are safer, more effective, and less expensive [6-7]. Plants have been used to make medicines for ages [8]. In the modern world, natural medications are becoming more popular to treat illnesses with fewer adverse effects and better therapeutic outcomes. The escape of human and veterinary drugs into the environment through a variety of channels, which has grown to be a significant concern for both human and environmental health, is another crucial reason for the shift from synthetic to herbal medications [9]. By blocking pro-inflammatory mediators and signaling pathways, Chebulinic acid (**Figure 1**), a naturally occurring compound found in many medicinal plants, especially *Terminalia chebula* (also known as black myrobalan, King of medicine, or Haritaki) [10], exhibits anti-inflammatory and antioxidant [11] properties, making it useful in the treatment of ailments like arthritis [12], anti-ulcer activity [13], and inflammatory bone loss [14]. It may operate as a prodrug in terms of anti-ulcer action, causing prolonged stomach retention. When taken orally, *Terminalia chebula* extract, primarily used in Ayurvedic herbal treatments, shows dose dumping, reduced bioavailability, safety, efficacy, and degradation during immersion [15-16].

Chebulinic acid's strong hydrophobicity and poor aqueous solubility limit its utilization in the pharmaceutical industry despite its enormous potential in GI disorders [17]. The patient receives these herbal medications via an antiquated and traditional drug delivery mechanism, which reduces the drug's effectiveness and lowers its blood level below the therapeutic concentration, producing little to no therapeutic impact. Recently, there has been increased interest in novel herbal medicine delivery systems for delivering active ingredients found in herbal plants [18]. The issues with crude plant extracts, such as *Terminalia chebula* extract, are reduced when plant actives are incorporated into innovative drug delivery systems [19]. To maximize the effectiveness of Chebulinic acid against stomach issues, a novel formulation with improved water solubility and extended gastrointestinal residence duration is therefore significantly required. The gastroretentive drug delivery system (GDDS), which includes expandable, floating, and bio-adhesive (or mucoadhesive) systems, was developed recently to help patients with gastric diseases maintain drug localization in the stomach, overcome low drug efficacy, and extend dosing intervals [20]. Low-density systems that have the highest buoyancy for floating on gastric material and stay for extended periods of time in the stomach are known as floating systems. The medicine is given continuously at the desired pace during the system hangover of the stomach contents, increasing gastric retention time and reducing volatility [21]. It is unusual for floating systems to create sustained buoyancy of drugs in the stomach without changing the gastric emptying time in any particular way. A longer gastric retention period produces the intended delayed drug release rate from the system and offers considerable control over changes in drug plasma concentrations [22]. Providing adequate stomach fluid saturation to maintain the buoyancy of the dose form is a significant disadvantage or restriction of such systems. Bioadhesive polymers are used to address this problem; they adhere to the stomach mucosal lining because of their unique, natural behaviour. Because of their involvement in the formulation of dosage forms, medications with absorption windows in upper GIT exhibit better bioavailability, lowering drug frequency. Mucoadhesive delivery devices address the problem of GIT transit time reduction. Because of their propensity for adhesion, these polymers are sufficiently compelling to increase the adhesiveness of the dosage form. These polymers, including synthetic and natural mucoadhesive polymers, have enhanced the literature [23]. This research aims to formulate floating, mucoadhesive microspheres that contain extract from *Terminalia chebula*. Eudragit S100 and ethyl acetate were used to create microspheres in the solvent evaporation process. Because of a lower frequency of administration, the assisted benefits would be mirrored to provide better patient compliance.

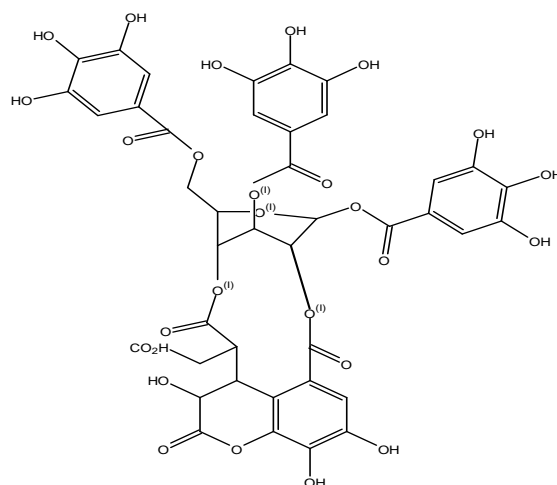


Figure 1: Structure of Chebulinic acid.

2. Materials and Methods

2.1 Chemicals

Chebulinic acid was acquired from Phisic herbals as a gift sample, *Terminalia chebula* Fruit was purchased from the local market, Research lab fine chem. Industries provided Eudragit S100. Titan Biotech supplied ethyl cellulose, ethanol, n-hexane, and acetone. Ltd, Changshu Hongsheng fine chemical co. Ltd., Qualikems Fine Chem Pvt. Ltd., and LobaChemie Pvt. Ltd. Respectively, PVA and Dichloromethane were procured from Thermo Fisher Scientific India Pvt. Ltd. and hydrochloric acid as well as sodium hydroxide were supplied by Nice Chemicals Pvt. Ltd.

2.2 Preparation of Extract

The extract was prepared using the maceration technique (**Figure 2**). *T. chbula* fruits were cleaned and dried under shade, followed by powdering (coarse powder). The fruit powder was macerated with 70% v/v ethanol for 48 h, and the extract was dried under vacuum and then stored in a tight amber glass bottle at 40C for further studies [24].

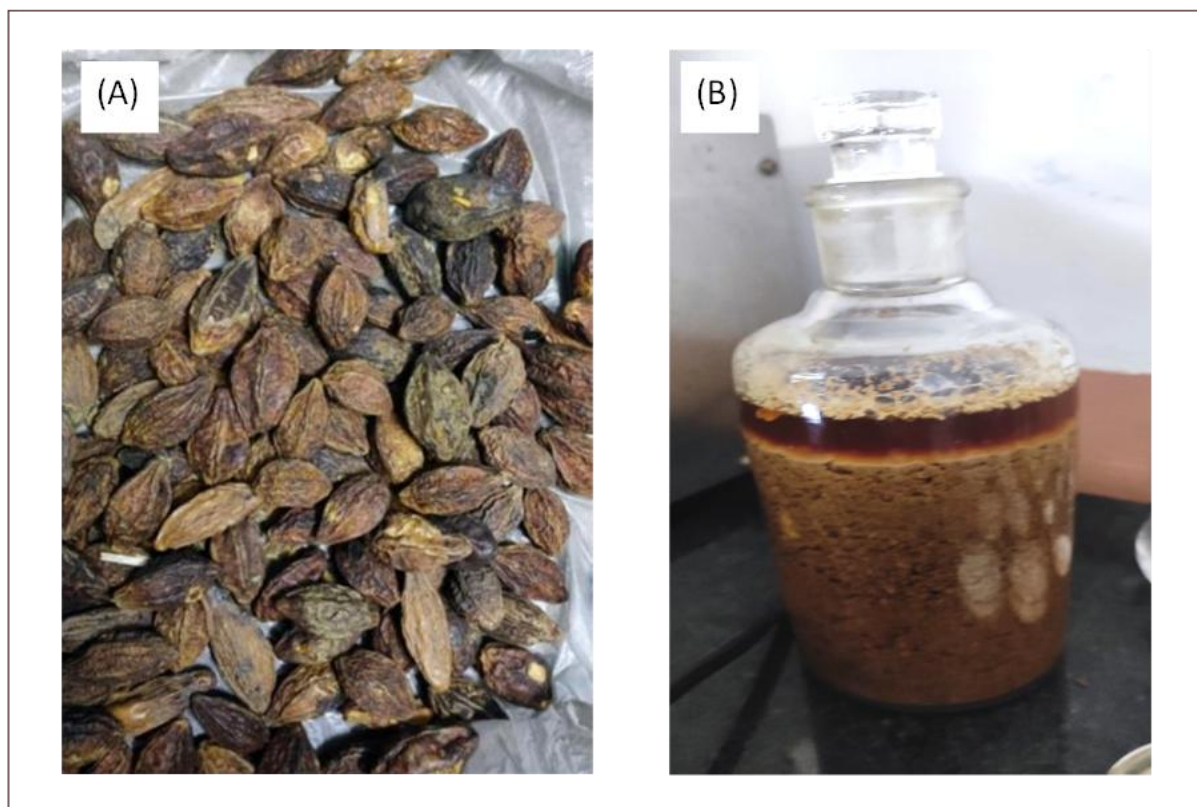


Figure 2: (A) Dry fruit of *Terminalia chebula* (B) Preparation of Extract (maceration technique).

2.3 Preparation of Floating Microspheres

A solvent evaporation technique was employed to formulate microspheres (**Table 1**). At room temperature, the drug and polymer were mixed in a solvent (dichloromethane: ethanol; 1:1). The prepared slurry was allowed to be mixed in 100 ml of 1% w/v polyvinyl alcohol (emulsifier). The system was stirred using a mechanical stirrer for three hours at room temperature to evaporate solvents and subsequently stored in desiccators [25].

Table 1: Composition of *T. Chebula* extract microspheres.

| Components | Formulation Code | | | |
|----------------------------------|------------------|-----|-----|-----|
| | F1 | F2 | F3 | F4 |
| <i>T. Chebula</i> (Extract) (mg) | 200 | 400 | 400 | 200 |
| Ethyl cellulose (mg) | 200 | 400 | 200 | 400 |
| Eudragits100 (mg) | 200 | 400 | 200 | 400 |
| Ethanol (ml) | 10 | 10 | 10 | 10 |
| Polyvinyl alcohol (w/v%) | 1.5 | 1.5 | 1.5 | 1.5 |

2.4 Pre-formulation Study of Extract

A pre-formulation study is an analysis of active ingredients' chemical and physical characteristics and additives. It serves as the base for preparing safe and efficacious dosage forms. After procuring the drug, a pre-formulation study was conducted [22]. Organoleptic properties, melting point, and calibration curve of prepared extract and chebulinic acid were determined. The study aimed to generate valuable information for the preparation of stable and bioavailable dosage forms.

2.5 Surface Morphology by SEM

Morphological characterization of the microspheres was carried out using scanning electron microscopy (SEM) under higher and lower resolution [26].

2.6 Micromeritic Properties of Prepared Microspheres

Bulk density, tapped density, angle of repose, carr's index, and Hausner's ratio were determined using formulas mentioned in **Table 2** [27].

Table 2: Formulas to calculate micrometric properties of prepared microspheres.

| Property | Formula Used |
|----------------------------|--|
| Bulk density | Powder weight/ bulk volume |
| Tapped density | Powder weight/ bulk volume |
| Hausner's ratio | Tapped volume/ bulk volume |
| Carr's index | Tapped density- bulk density/ tapped density 100 |
| Angle of repose (ϕ) | \tan^{-1} height of heap/ radius of the heap |

2.7 Percentage Yield

It was calculated by multiplying the dried microspheres' weight obtained through each batch by the initial weight of the started material sum. The % yield was determined by the following formula [26].

$$\% \text{Yield} = (\text{weight of product}) / (\text{Total weight of excipients and drugs}) \times 100 \dots \dots \dots (1)$$

2.8 Particle Size

The molecule size of microspheres was observed using an optical microscope. Eyepiece micrometers were aligned with the assistance of stage micrometers. The standard molecule size of the microspheres was dictated using Edmondson's equation [28].

$$D_{\text{mean}} = \frac{\sum d^n}{\sum n} \dots \dots \dots (2)$$

Where n = Number of microspheres, d = mean size range.

2.9 Drug Entrapment Efficiency

Microspheres equivalent to 10 mg of chebulic acid were crushed using a mortar pestle and suspended in 25 ml of 0.1N HCl. After 24 hours, it was filtered, and from the filtrate, 1 ml was taken and diluted to 25 ml. It was then scanned using a UV spectrophotometer at 280 nm. The drug entrapment efficiency was calculated using the formula [29].

$$\% \text{ Drug entrapment efficiency} = (\text{Practical drug content}) / (\text{Theoretical drug content}) \times 100 \dots \dots \dots (3)$$

2.10 Buoyancy Study

10 mg of sample was allowed to mix with 50 ml of 0.1 N HCl containing 0.2% w/v tween 80 at 100 rpm on the magnetic stirrer. The layer of buoyant microspheres was pipetted out and separated by filtration after 8 hours. Also, particle sinks were separated and dried in a vacuum desiccator. Both the fractions of microspheres were weighed, and buoyancy was calculated by following the formula;

$$\% \text{ Buoyancy} = W_f / (W_f + W_s) \times 100 \dots \dots \dots (4)$$

W_f and W_s are the weights of the floating and settled microparticles, respectively [21].

2.11 In-vitro Drug Release

Drug release was carried out using a basket-type apparatus, 0.1N HCl (pH 1.2) as a medium, and for 8 hours. 120 mg of sample was used for the study, and the assembly temperature was maintained at $37 \pm 0.5^\circ\text{C}$ with 100 rpm speed. During the study, sink conditions were maintained. A 5 ml sample was withdrawn at a 60 min time interval; the initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal, passed through a $5 \mu\text{m}$ membrane filter, and analyzed spectrophotometrically at 280 nm [30].

2.12 In-vitro Mucoadhesive Test

The mucoadhesive properties of the discs were tested by ex vivo adherence. A newly cut piece of goat intestinal mucosa (3 cm long) was inserted into the microscope slides with cyanoacrylate glue. Slides of the microscope were attached to the tablet disintegration apparatus (USP). A sample was given a slow, usual moment of ascent and descent of the test liquid (900 ml of 0.1 N HCl) at $37 \pm 0.5^\circ\text{C}$ and hourly intervals of up to 6 hrs. The machine was stopped, and the test was carried out in triplicate [34].

$$\% \text{ Mucoadhesion} = (\text{Total no of microspheres remains}) / (\text{Total no of applied microspheres}) \times 100 \dots \dots (5)$$

2.13 Release Kinetics Studies

To analyze the in-vitro release data, various kinetic models were used to describe the release kinetics, including a zero-order release model, a first-order release model, a Higuchi model, a Hixson-Crowell cube root law, and a Korsmeyer-Peppas model [31].

3. Results and Discussion

3.1 Pre-formulation Studies

Various tests were used to analyze the organoleptic properties of *Terminalia chebula* extract and chebulinic acid, which were found to be a dark brown color and white color, respectively. Both were found to be odorless with a slightly bitter taste. The melting point of chebulinic acid was observed at $234 \pm 5^\circ\text{C}$. λ_{max} represents the wavelength of light in the ultraviolet region at which the compound exhibits maximum absorbance. Maximum absorbance of *Terminalia chebula* extract and Chibulinic acid was observed at 280nm and 230 nm, respectively, and at these wavelengths, calibration curves were taken. Here, marketed chebulinic acid was used as a standard to confirm its presence in the prepared extract. The correlation coefficient of *Terminalia chebula* extract (R^2) was found to be 0.998 with regression line equation: $y = 0.024x + 0.0017$, regressed line slope = 0.024, where (y) absorbance, (x) concentration ($\mu\text{g/ml}$) (**Figure 3A**). Also, the Correlation coefficient of chebulinic acid (R^2) was found to be 0.999 with the regression line equation: $y = 0.048x + 0.0018$ and regressed line slope = 0.048 (**Figure 3B**).

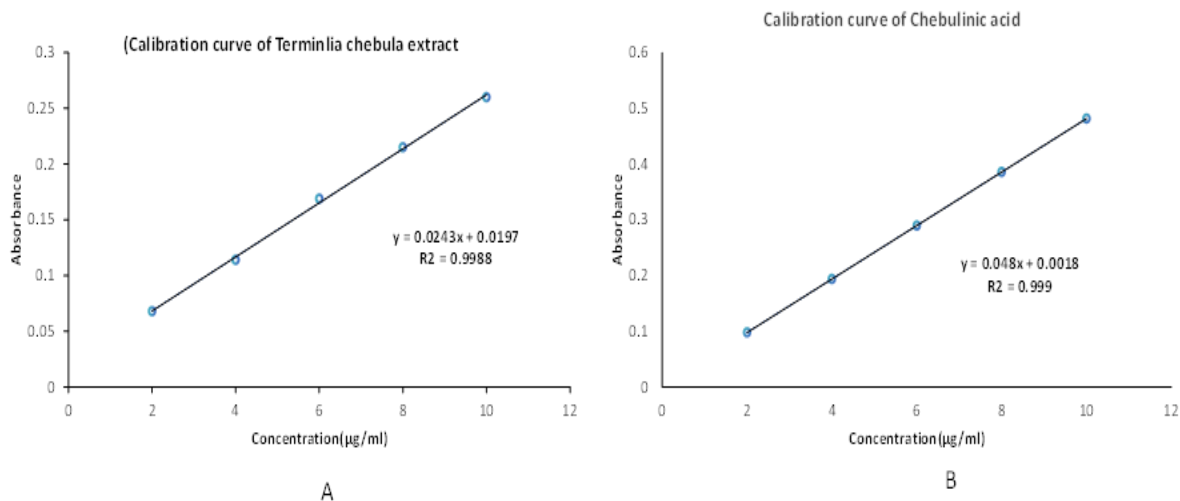


Figure 3: Calibration curves of (A) *Terminalia chebula* extract; (B) chebulinic acid.

3.2 SEM Study

SEM detected surface morphology for prepared microspheres, revealing a rough surface (**Figure 4**).

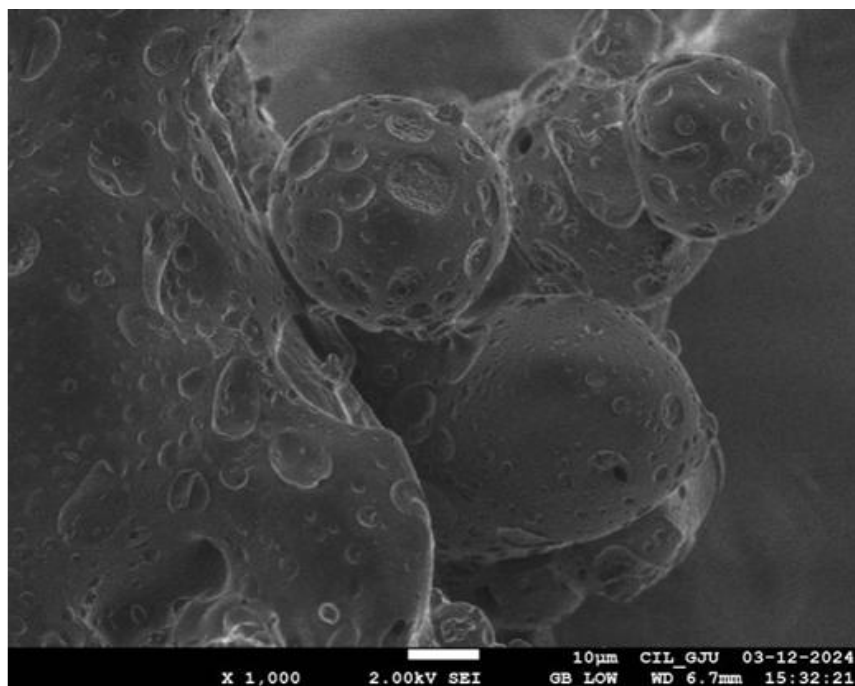


Figure 4: Surface methodology of microspheres using SEM.

3.3 Micromeretic Properties of Microspheres

Prepared microspheres were characterized for bulk density, tapped density, Carr's index, angle of repose, and Hausner's ratio (**Table 3**). The angle of repose ranged from 23070' to 30096'. F2 had the best micromeretic properties depicting good flow, Hausner's ratio (1.15), Carr's index (less than 35%), and angle of repose (28029') [33].

Table 3: Results of micrometric evaluations of floating-mucoadhesive microspheres.

| Formulation Code | Bulk density (g/cm ³) | Tapped density (g/cm ³) | Carr's index (%) | Angle of repose | Hausner's ratio |
|------------------|-----------------------------------|-------------------------------------|------------------|-----------------|-----------------|
| F1 | 15.23 | 19.04 | 11.04 | 23°70' | 1.25 |
| F2 | 68.51 | 78.91 | 33.25 | 28°29' | 1.15 |
| F3 | 44.78 | 53.74 | 52.90 | 29°74' | 1.20 |
| F4 | 54.58 | 90.96 | 30.95 | 30°96' | 1.66 |

3.4 Physio-chemical Evaluation of Microspheres

Various tests, including particle size, percentage yield, drug entrapment, and buoyancy study, were carried out for the physicochemical evaluation of formulations (**Table 4**).

Table 4: Results of average particle size, percentage yield, in-vitro buoyancy, and entrapment efficiency of formulation.

| Formulation Code | Average Particle Size (µm) | Percentage Yield (%) | In-vitro Buoyancy in 8 hours (%) | Entrapment efficiency (%) |
|------------------|----------------------------|----------------------|----------------------------------|---------------------------|
| F1 | 100.08±0.95 | 88.68 | 87.66 | 91.94 |
| F2 | 160.24±0.78 | 74.16 | 89.39 | 77.34 |
| F3 | 310.32±0.20 | 72.02 | 75.43 | 67.11 |
| F4 | 200.51±1.23 | 74.30 | 77.96 | 71.94 |

Mean particle size of formulations F1 (100.08±0.95) to F4 (200.51±1.23) containing different polymers concentration. Particle size distribution and shape results are shown in **Figures 5** and **6**, respectively.

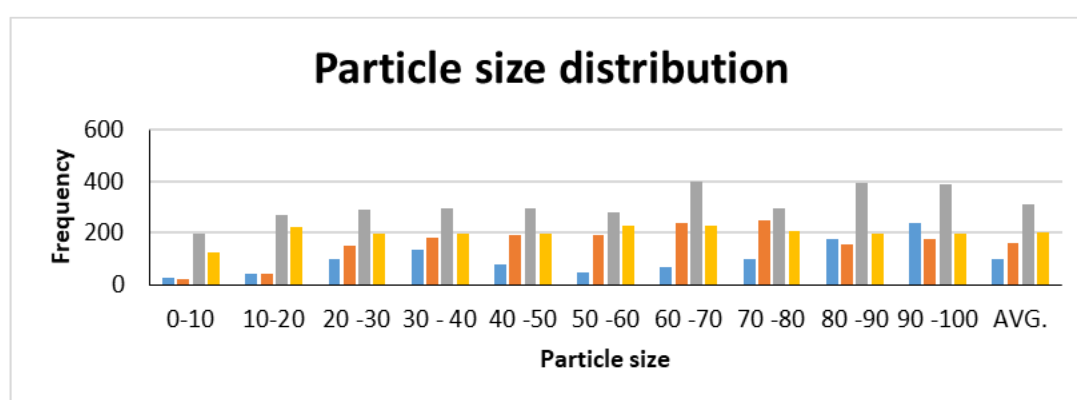


Figure 5: Particle size distribution under the compound microscope.

Results revealed that particle size increased by increasing the drug-to-polymer ratio from 1:1 to 1:2. Also, extract concentration (1:1 to 1:2) directly enhanced particle size. Formulated microsphere formulations yielded the highest percentage yield for F1 (86.685). With the increase in polymer concentration, yield increased.

Results revealed that the percentage yield decreased when polymer and extract concentration increased from 200 mg (F1, F4) to 400 mg (F2, F3). Drug entrapment and buoyancy decreased with a reduction in extract concentration, and F1 (91.94%) showed maximum entrapment. Also, F1 and F2 revealed buoyancy greater than 80% after 8 hours, leading to satisfactory performance.

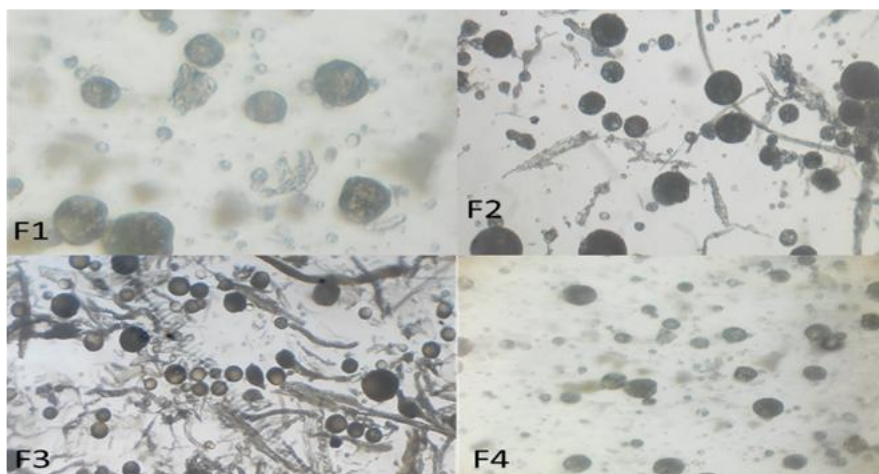


Figure 6: Different formulations of particle shape and size distribution using an optical microscope.

3.5 *In-vitro* Drug Release

Drug *in-vitro* release of formulations was found to be F1 (98.48), F2 (94.78), F3 (91.31), and F4 (92.22); F1 was found to have the best release of CA(98.48%) for an extended period (after 8 hours). Also, F1 showed the best cumulative release compared to F2, F3, and F4 formulations (**Figure 7**). It was revealed from the data that with an increase in polymer concentration from 200 mg each (F1) to 400 mg each (F2), *in-vitro* release decreased. Also, with an increase in extract-to-polymer ratio from 1:1 (F1) to 2:1 (F3), *in vitro*- release was significantly reduced, indicating a direct relation with extract concentration.

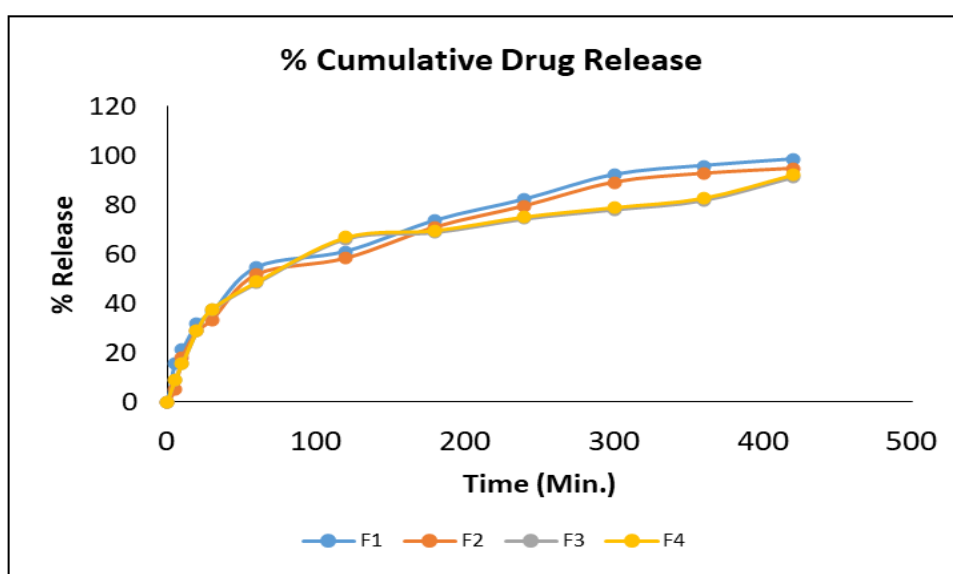


Figure 7: Percentage cumulative release curve for different formulations of prepared microspheres.

3.6 *In-vitro* Mucoadhesive Study

An *in-vitro* adhesion test was employed for 6 hours in the mucoadhesive study (**Figure 8**). F1(62%) showed the highest mucoadhesive property, having a polymer ratio of 1:1. Further, with different ratios, the *in vitro* mucoadhesive property was reduced from F2(58%)> F3(50%)> F4(54%).

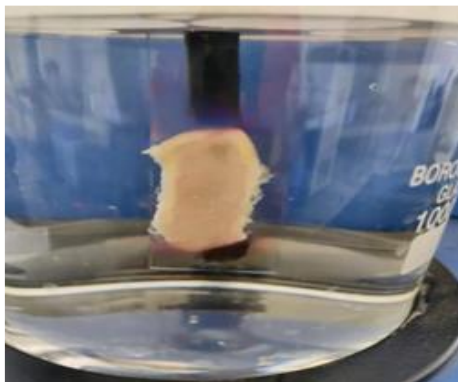


Figure 8: Microscope slides with micro-particles for mucoadhesive testing.

3.6 Release Kinetics

In-vitro release data were applied to a zero-order, first-order Higuchi, Korsmeyer—Peppas, and Hixson Crowell kinetic model to predict release mechanisms and kinetics. The Hixson Crowell model best explained the release mechanism, as R² values were found to be 0.9604.

4. Conclusion

By employing the solvent evaporation approach, it is achievable to successfully synthesize floating-mucoadhesive microspheres of *Terminalia chebula* using Ethyl cellulose, Eudragit S100, and PVA as polymers. Additionally, it was determined that the description, colour, and distinctive smell of *Terminalia chebula* were disclosed by organoleptic investigations. Chebulinic acid was detected in the *Terminalia chebula* extract by FTIR analysis. With the increase in polymer concentration, there was a considerable rise in particle size, percent yield, and percent buoyancy. Following IP specifications, pre-formulation experiments were conducted involving organoleptic bulk density, tapped density, angle of repose, Hausenr's ratio, and melting point range. The F1 formulation was shown to have the best *in vitro* release and maximal drug entrapment. Mucoadhesive property was highest in F1. Hixson Crowell's model provided the best explanation of the drug release process. The lack of adequate clinical research is impeding the development of this practical drug molecule as a more effective therapeutic option, even though numerous herbal formulations have been described in the literature to have potential therapeutic effects.

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It was declared to be none.

Conflict of interest

It was declared to be none.

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