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EXPLORING THE POTENTIAL OF CARBOCISTEINE LOADED MICROPARTICULATE SYSTEM BY USING CCD MODEL FOR THE TREATMENT OF RESPIRATORY INFECTIONS

Mayur R. Gavit, Bhushan R. Rane*, Vaibhav L. Patil, Nandini R. Mhatre, Ashish S. Jain

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ABSTRACT
Background: Multi-particulate drug delivery systems (microbeads) deliver drugs over an extended period, distributing them evenly throughout the gastrointestinal tract and minimizing local irritation. Microbeads are small, solid, free-flowing particulate carriers that contain drug particles that have been dispersed and are either crystalline in solution. **Aim:** The present work explores the potential of the carbocisteine-loaded floating microparticulate drug delivery system. **Methodology:** Floating microbeads were prepared using the ionotropic gelation method and optimized using Central Composite Design. **Result and discussion:** Floating microbeads of prepared carbocisteine were evaluated for the FTIR study, which reveals no interaction between the drug and other excipients. Buoyancy time, drug content, particle size, and % drug release were also characterized; it found that drug release was 90.24 %, up to 17 hours, 250 to 220 µm, and drug content 96.67%, respectively, for the optimized batch. An accelerated stability study was performed, showing that the formulation was stable. Floating microparticulate drugs were prepared, and batch B-3 was optimized based on in-vitro buoyancy and release patterns. The floating ability of the beads was observed visually for 10 to 17 hr, and an increase in polymer concentration decreased the swelling of the beads. **Conclusion:** The results obtained from the formulation batch B-3 show good results for all the parameters tested. Floating microbeads could be the best possible approach to deliver drugs with the benefit of reduced dosing frequency.

INTRODUCTION

Most multi-particulate drug delivery methods are oral dosage forms of several tiny, distinct units, each possessing a few desired properties. Multiparticulate dosage forms are pharmaceutical formulations where the active ingredient is present as several small independent subunits. In these systems, the dosage of the pharmacological ingredients is divided into a plurality of subunits, often consisting of thousands of spherical particles [1]. These subunits are compressed or encapsulated into a tablet and placed into a sachet to produce the total dose. The system's foundation is the core's expansion (non-effervescent FDDS or low-density approach), which causes floating because of low density [2]. Moreover, the buoyancy of these dosage forms is provided by the air trapped by the inflated polymer [3].

*Department of Pharmaceutics, Shri D. D. Vispute College of Pharmacy & Research Center, Panvel, Dist. Raigad, India-410206

***For Correspondence:** **rane7dec@gmail.com**

Small, solid, free-flowing particulate carriers called microbeads hold dispersed medication particles in crystalline or solution form, enabling different release profiles or a prolonged release of active ingredients without significant adverse effects [4]. The beads can also include drugs to deliver them locally at high concentrations, ensuring therapeutic amounts are achieved at the target site and minimizing side effects by maintaining low systemic concentrations. They also retain their effectiveness under physiological settings [5]. The most ideal method of administering medication is by far oral drug delivery. Unfortunately, the therapeutic potential of many medications is limited by their half-lives in circulation and limited absorption via a specific intestinal segment. Achieving a therapeutic impact sometimes requires regular dosage of drugs due to pharmacokinetic limitations [6]. The patient complains as a result of the pill load this causes. Delivering the medication in a controlled, site-specific way increases bioavailability and optimizes the pharmacokinetic and pharmacodynamic characteristics. One micron, or one-thousand of a millimeter, to several millimeters, is the size range of microparticles, a form of medication delivery device [7].

Microencapsulation technology, medications can be stabilized, incompatibilities can be removed, unwanted tastes can be covered up, and drugs can be protected from the environment. As a result, they are crucial as drug delivery methods that reduce adverse effects and increase the bioavailability of traditional medications. Beads are solid, free-flowing, almost spherical particulate carriers that carry scattered drug particles in either crystalline or solution form. The size of beads ranges from 0.5 to 1000μm [8]. Polymers, including anionic (like sodium alginate) and cationic (like chitosan), are used to make beads. Calcium alginate-chitosan beads, calcium alginate-xanthan gum beads, and calcium alginate-maltodextrin beads are the three different alginate beads. Enteric-coated alginate beads demonstrated prolonged release and targeted medication delivery to the body when coated with cellulose acetate phthalate (CAP), a pH-sensitive polymer. A naturally occurring hydrophilic biopolymer derived from algae and brown seaweed, sodium alginate is a polysaccharide. The ionotropic gelation process may create beads using one of two sub-methods. The cross-linking ion's source varies across the techniques. One of the approaches places the crosslinker ion outside the polymer solution, while the other incorporates it inside the solution in an inactive state [9]. Hollow microspheres, also known as floating microspheres. In a literal sense, hollow microspheres are spherical, empty particles without a core that are free-flowing powders made of artificial polymers or proteins and preferably have a size between one and a thousand micrometers. Low-density devices known as gastro-retentive floating microspheres possess enough buoyancy to float over gastric contents and stay in the stomach for extended periods.

Several gastro-retentive dose forms, such as pills, tablets, laminated films, floating microspheres, granules, and powders, can be found. The homogeneous distribution of these multiple-unit doses in the stomach, which leads to more consistent drug absorption and a lower risk of local discomfort, has drawn attention to floating microspheres. When the medicine is delivered gradually at the intended part, there are fewer variations in the plasma drug concentration and more stomach retention. By reducing the frequency of administration, floating microspheres can increase patient compliance and improve the therapeutic efficacy of short-half-life medications [10].

MATERIAL AND METHOD

Micro Labs Pvt. Ltd. Mumbai, India, provided Carbocisteine as a gift sample. HPMC K4M, HPMC K15M, Eudragit S100, and calcium chloride were purchased from Research-Lab Fine Chem Industries, Mumbai.

The rationale behind the selection of polymer

In current research work, Eudragid S100, HPMC K4M, and HPMC K15M have been selected as polymers for the microencapsulation of the drug. The main objective is to release drugs in a sustained manner. The literature survey observed that the other polymers could show the sustained release of drugs up to a maximum of 5 to 6 hours, and drug entrapment was also decreased, while selected polymers can show release to maximum hours with more entrapment. The HPMC is a swellable polymer with more sustained release than Eudragit S100 (soluble above pH 5.5). Also, a higher viscosity grade of HPMC (HPMC K15M) shows higher entrapment of the drug. Thus, HPMC K15M is selected for further studies.

FTIR Study

FTIR Spectrophotometer (Shimadzu, 00693) was used to perform IR spectra of medication and bead composition. The sample (1mg) was combined with the dried powdered potassium bromide (10mg). The powdered combination was placed in a

sampler, and an FTIR spectrophotometer was used to record the spectra by scanning the wavelength range of 4000-400 cm-1. To determine if interactions exist and to identify changes in functional groups, an FTIR spectrum is utilized [11].

Method of preparation of floating microbeads

Using varying proportions of polymers, the Ionotropic Gelation technique was used to create the carbocisteine floating microbeads **(Figure 1)**. A sodium alginate solution was added to 100 ml of purified water. After being triturated, a measured amount of carbocisteine, HPMC K4M / HPMC K15M / Eudragit S100, was added to the sodium alginate solution above and thoroughly mixed. The abovementioned solution was added to 100 ml of gently stirred calcium chloride (5% w/v) solution to create microspheres using a 21 gauge no. syringe needle. The solution containing the microsphere was gently moved using a magnetic stirrer for about 10 minutes. The microspheres were left in the same solution for an additional twenty minutes to increase mechanical strength. After being filtered and cleaned with distilled water, the microspheres were allowed to air dry at room temperature before being stored [12]. The composition of each dried mixture is shown in **Table 1**.

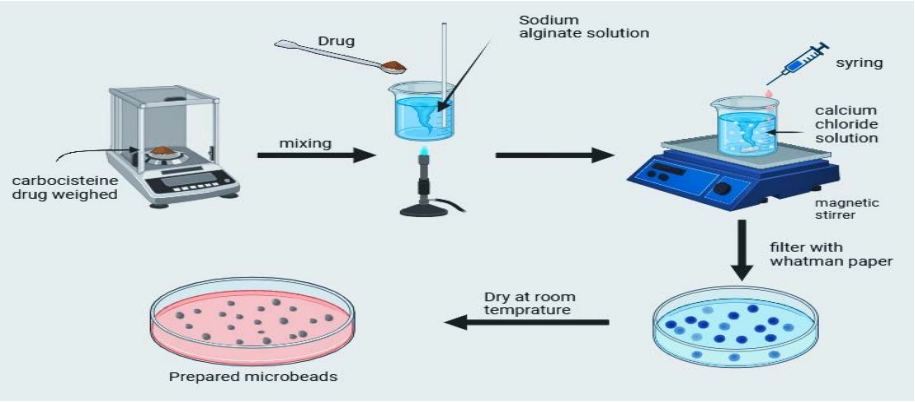

Figure 1: Method of preparation of floating microbeads

Table 1: Primary formulation table for floating microbeads

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	150	150	150	150	150	150	150	150	150
Sodium alginate (%)	1	1.50	2	1	1.50	2	1	1.50	2
HPMC k15M (mg)	150	300	450	-	-	-	-	-	-
HPMC K4M (mg)	-	-	-	150	300	450	-	-	-
Eudragit S100 (mg)	-	-	-	-	-	-	150	300	450
Calcium chloride (%)	5	5	5	5	5	5	5	5	5

Optimization of formulation

Central composite design

Preliminary investigations were conducted to determine the quantities of variables for additional research, concentrating on the bead production and floating qualities. To study the variables, all batches were prepared according to Central composite design (CCD), and the effect of independent variables (conc. of HPMC K15M and conc. of sodium alginate) was analyzed on dependent variables (%EE, floating time, and % yield). The factors were studied at three different levels (+1, 0, -1) for factor 1 (conc. of HPMC K4M) (150mg, 300mg, 450mg) and factor 2 (conc. of sodium alginate) (1%, 1.5%, 2%) respectively. The minimal experimentation center point was repeated five times, and the mean of all five was used in additional research. This DoE (design expert 13.0.5.0) is the most effective design in evaluating the influence of individual variables (primary effects) and their interactions. The dependent variables were floating time, drug entrapment efficiency, and yield percentage [13]. Different batches were made, as indicated in **Table 2**.

Characterization of floating microbeads

The manufactured floating beads were assessed for in vitro drug release, micrometric studies, yield, encapsulation efficiency, swelling, and FTIR and short-term stability studies [14].

Physical Appearance

Every batch of carbocisteine beads was examined for both color and physical characteristics.

Micromeritic Studies of Floating Microbeads

Floating microbeads are characterized by their micrometric properties, such as bulk and tapped density, compressibility index, and flow properties.

Table 2: Variables and responses of QBD selected compositions of variables

Run	Factor 1	Factor 2	Response 1	Response 2	Response 3
1	150	2	70.21	8	68.56
2	300	1.5	81.5	11	74.22
3	300	1	79.63	10	72.11
4	300	2	84.02	12	78.34
5	300	1.5	83.15	11	74.53
6	300	1.5	81.03	12	76.23
7	300	1.5	80.9	10	76.1
8	300	1.5	82.61	13	75.34
9	450	2	90.24	17	80.71
10	150	1.5	71.61	9	70.23
11	150	1	75.89	7	66.25
12	450	1	84.79	13	76.89
13	450	1.5	86.54	15	75.83

Bulk and tapped density

A 5 ml graduated cylinder was used to test the densities of both bulk and tapped materials. After the sample was put into the cylinder and mechanically tapped 100 times, the bulk and tapped densities were calculated, and the tapped volume was recorded.

Bulk density = Mass of Formulation / Bulk Volume.

Tapped density = Mass of Formulation / Tapped Volume [15]

True density

Using water as the immersion fluid and the liquid displacement technique, the true densities (D_T) were calculated using the following formula [12].

$D_T = W [(a + w) - b] X SG$

Where a is the weight of the bottle plus liquid, b is the weight of the bottle plus solvent plus powder, w is the weight of the powder, and SG is the specific gravity of the liquid [10].

Carr's Compressibility (C.I.)

The value of microbeads' Compressibility index (C.I.) or Carr's index was calculated using the formula below.

C.I. = tapped density – bulk density / tapped density × 100

A powder that often results in strong flow characteristics has a range below 15%, whereas a number above 25% indicates poor flow ability [16].

Hausner's ratio

By utilizing the equation to compare the tapped density to the bulk density, one may find Hausner's ratio of microbeads:

Hausner's ratio = tapped density/bulk density [17].

Porosity

The porosity of the floating microspheres was determined by a helium pycnometer and calculated by using the following equation [10]:

% porosity = true density-bulk density/true density X 100

Angle of repose (θ)

The greatest angle between the surface of a powder pile and a horizontal plane is the angle of repose. Different formulations' angles of repose were calculated using the fixed funnel standing technique. The beads were placed on a piece of plane paper that was held horizontally and let drip out of the funnel aperture. This causes a bead pile to appear on the paper. The following equation was used to compute the angle of repose by changing the values of the base radius (r) and pile height (h), $\tan \theta = h / r$,

Where θ is the angle of repose, h is the height, and r is the radius [18].

Drug content

A predetermined quantity of medication-containing microbeads is dissolved in an appropriate solvent, such as methanol or ethanol. Next, a 5 µm membrane filter is used to filter the mixture. Finally, the HPLC (HPLC Agilent Technologies 1260 infinity II) determines the amount of drug content [17]. The following formula is used to determine drug content:

% drug content=weight of the drug in microbeads/weight of microbeads recovered X 100

Entrapment Efficiency

The sample was analyzed using (HPLC Agilent Technologies 1260 infinity II) at 220 nm after precisely weighed amounts of around 50 beads were crushed using a mortar and pestle and dissolved in 50 ml of 0.1N HCl (pH 1.2). The proportion (w/w) of the theoretical drug content was used to calculate encapsulation efficiency [19].

Drug Entrapment efficiency = (Practical drug content/ Theoretical drug content) x 100

Buoyancy studies

The prepared beads were assessed using the (USP dissolution apparatus type-2 lab India DS 8000) for buoyancy and floating time. After agitating the 900 ml of 0.1N hydrochloric acid at 100

rpm and placing twenty beads from each batch, the temperature was maintained at 37°C ± 2°C for the duration of the research and the amount of time needed for beads to float to the top (floating lag time). The beads' float capacity was visually monitored for a day [19].

% Yield

% Yield for the different formulations was calculated using the formula below [19].

% Yield =Total weight of floating beads produced ×100 / Total weight of drug and polymer

DSC Study

DSC-1 Systems were employed in the DSC analysis. Samples (2–5 mg) were heated in an open aluminum pan at 100°C/min throughout a temperature range of 30 to 320°C under a 2-bar pressure nitrogen flow. DSC was used to examine the phase equilibrium, polymorphic changes, melting and crystallization, and decomposition behavior of alginate beads. As a result, the DSC was used to describe the complex [20].

Stability study

Stability investigations were conducted at 40°C and 75% relative humidity for three months. The final glass containers, tinted amber, were filled with the chosen composition and securely sealed with a cap. For 90 days, they were kept at 40 °C±2 °C/ 75% ± 2% RH. After three months, samples were examined for in vitro drug release research and percentage drug entrapment [21].

In vitro drug release study

The drug release was investigated using a (USP dissolution apparatus type ii lab India DS 8000) at 100 rpm in a 0.1 N HCl solution as the dissolving medium (900 mL) kept at 37 ± 5°C. Every hour, a sample (10 mL) of the solution was taken out of the dissolving equipment for up to 17 hours, and the samples were replaced with new dissolving media. After filtering, the samples were diluted with 0.1 N HCl solution to the appropriate concentration. The sample was analyzed using (HPLC Agilent Technologies 1260 infinity II) at 220 nm. An equation derived from a standard calibration curve was used to determine the percentage of drug release [22].

RESULTS AND DISCUSSION

FTIR Study

The most important vibrational frequencies and their assignments are displayed in **Figure 2**, which displays the sample FT-IR spectrum of carbocisteine. C=O stretching is the vibrational assignment. Strong IR absorptions at 1635 and 1620.30 cm–1 appear in the FT-IR spectrum of carbocysteine, and they are representative of the asymmetric stretching vibrational mode of the carbonyl moieties found in the carboxylic acid group. stretching C–H Similarly, the C–S stretching vibrational frequency found at 1197.39 cm–1 and the two different peaks at 1665.15 cm–1 could most likely originate from the C–S bond's stretching mode. The structural identification of the experimental spectrum data was further checked against a standard of similar structures.

FTIR analysis was conducted to evaluate the compatibility of the optimized formulation of carbocisteine microbeads. The C-H stretching in the Carbocisteine FTIR spectra was identified at 1662.25 cm−1. The C=O stretching was measured at 1631.62 cm−1. The O-H stretching was found at 1625.80. The peaks that were attributable to C-S stretching were found at 1203.65 cm−1. The detected peaks, which agree with the usual reported peaks, validate the drug's purity. The FTIR data confirms the identification of carbocisteine, and the improved formulation shows no interactions between the medication and excipients.

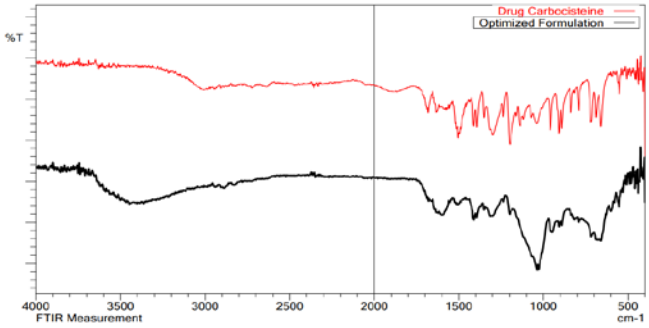

Figure 2: FTIR of drug and Optimized formulation of carbocisteine microbeads

Optimization of formulation using Central Composite Design

The results of the central composite design were assessed for R^2, adjusted R^2, and p-values of the model as quality indicators, as shown in Table 3. Figure 6 shows the desirability of independent variables on % EE, Floating time, and % yield.

% Yield

The % yield of all the selected 13 formulations was 66.25–80.71%, depending upon the variation in the independent variables. ANOVA analysis indicates that there was a significant effect of various independent variables on % yield. The linear equation of the selected model (R^2 = 0.8252, R^2 adjusted R^2 = 0.7502) indicating the effect on above mentioned variables is given below. The statistical analysis indicates that there was a

significant increase in the production yield (Y1) of the floating microspheres with an increase in the concentration of the polymer (F2) (p-value= 0.0002) and especially compared with HPMC (X1) (p-value=<0.0002). In contrast, the concentration of sodium alginate (F3) has no significant effect (p-value= 0.0208) on the % yield, as indicated by the positive coefficients in the regression equation, respectively.

$$58.6136 + 4.12 X A + 0.0315444 X B$$

From the Response surface plot **(Figure 3),** it was evident that the sodium alginate to polymers ratio (F2) positively affects the production yield of the floating microbeads. With the increase in the drug-to-polymers ratio, the production yield also increases. This effect can be explained by the increased throughput of the polymer slurry and rapid evaporation of the solvent. The product yield depended on the polymers (F1) to formulate F3. The yield of the microspheres containing less HPMC and more polymers was found to be increased. This may be due to the migration of HPMC into a continuous phase, forming agglomerates accompanied by the polymer being stuck to the stirrer blade and beaker surface.

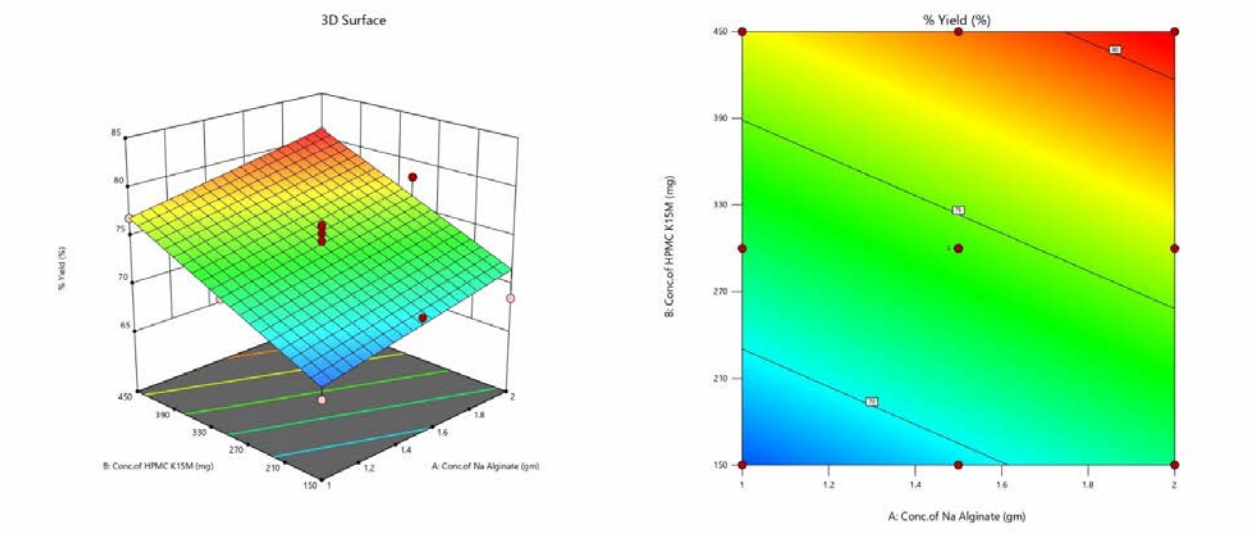

Figure 3: Effect of independent variables on % yield

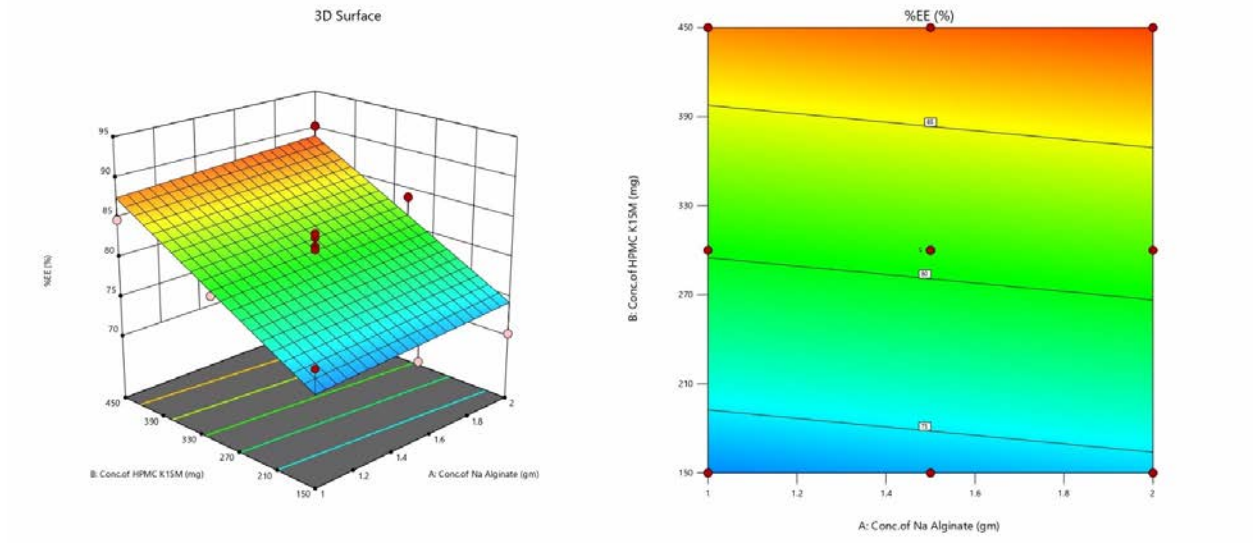

Figure 4: Effect of independent variables on entrapment efficiency

% Entrapment efficiency

The indirect method has been adopted to determine the %EE of carbocisteine in the microspheres. The response surface plot (**Figure 4**) indicates the effect of independent variables on the EE of prepared microspheres. Formulation 3 showed maximum entrapment of carbocisteine (90.24%). ANOVA analysis indicates that there was a high positive significant effect of the drug: polymers ratio (F2) (p-value= <0.001) and the concentration of PVA (F3) (p-value = < 0.0001) on carbocisteine entrapment efficiency while the effect of HPMC ratio (F1) is

insignificant on the EE of the RPD (p-value = 0.489). The linear equation of the selected model (R^2 =0.8523, R^2 adjusted R^2= 0.8228) indicating the effect on the above-mentioned variables is given below.

64.2323 + 1.38667 X A + 0.0487333 X B

It has been observed that the EE of the microspheres has been increased with an increase in the concentration of the polymers in the formulation (F3). This may be because, at higher concentrations of polymers, the drug available will be surrounded by an excess of polymer, resulting in better entrapment. The entrapment efficiency improved with increasing concentration of sodium alginate (F3) in the formulations. The increasing amount of HPMC might have increased the viscosity of the internal phase by arranging themselves in layers around the emulsion droplets. This conformation may have restricted the escape of carbocisteine until the droplets converted into floating microspheres.

In-vitro buoyancy

In-vitro buoyancy was determined for individual formulations; the in-vitro buoyancy of all the selected 13 formulations was in the 07-17 hours range. ANOVA analysis indicates that there was a high positive significant effect of the sodium alginate: HPMC ratio (F1) (p-value =0.0001) and sodium alginate: polymers ratio (F2) (p-value =0.0001). In contrast, the concentration of HPMC (F3) (p-value=0.0001) significantly negatively affects buoyancy. The variation in the buoyancy corresponds to different independent variables was explained by the given second-order equation

0.628205 + 2.33333 X A + 0.0244444 X B

(R^2=0.8952, Adjusted R2=0.8743) and presented by the response surface plot in **Figure 5**. The in-vitro buoyancy of microspheres can be correlated to the low density and insolubility of polymers in the simulated gastric fluid (pH 1.2). The buoyancy of particles depends on their density and size. The size of microspheres exhibited an inverse relationship to the microsphere density, and the buoyancy of microspheres increased with an increase in particle size, which can be directly related to the increase in the polymer concentration. The particles with a higher polymer ratio are less dense and more buoyant.

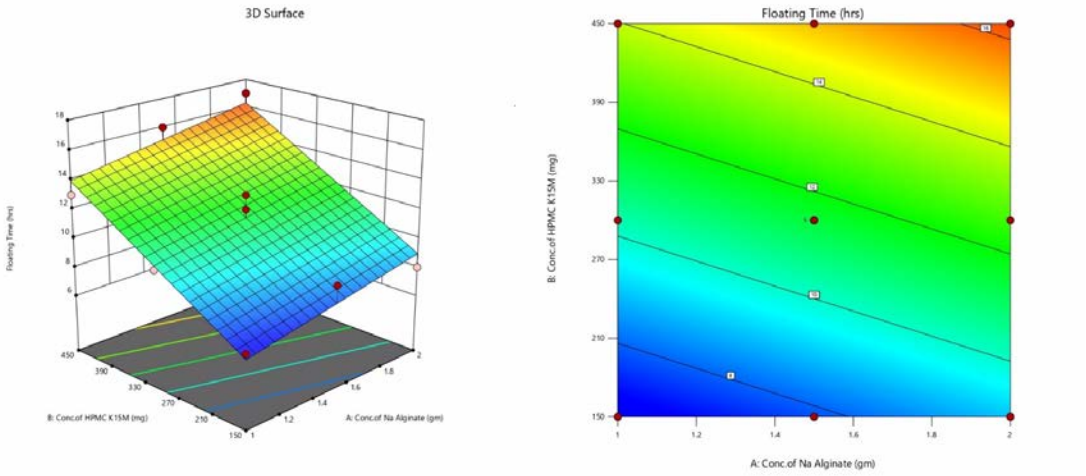

Figure 5: Effect of independent variables on floating time

Table 3: Regression values of the selected responses during optimization

Parameter	Linear model		
	% EE	**% yield**	**Floating study**
Std Dev	2.37	1.84	1.02
Mean	80.93	74.26	11.46
C.V %	2.93	2.48	8.90
R^2	0.8523	0.8252	0.8952
Adjusted R^2	0.8228	0.7502	0.8743
Predicted R^2	0.6503	0.6572	0.8188
Adeq. Precision	14.0737	15.3669	19.7344

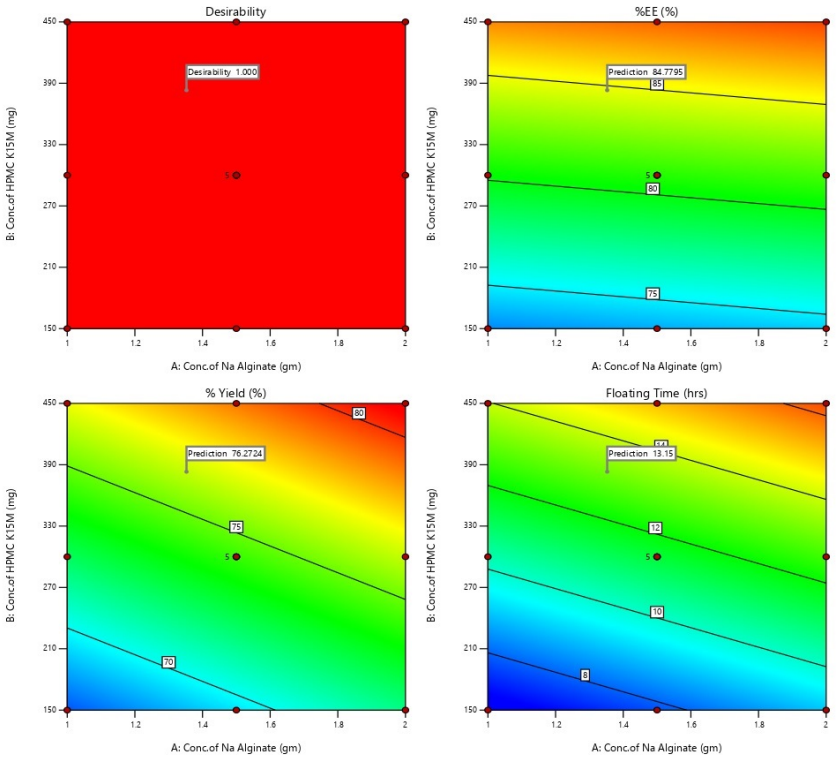

Figure 6: The desirability of independent variables: % EE, Floating time, and % yield

Micromeretic properties

Table 5 displays the mean particle size of the microbead formulations (F1-F9), which ranged from 240 (±0.0.5) to 2245 (±0.0.2). Particle size increased with increasing polymer concentration in both the original and modified batches. As the concentration of the polymer increases, the solution's viscosity also rises, increasing interfacial tension. Particle size rises because shearing effectiveness decreases with increasing viscosities. Hausner's ratio (F1-F9)(0.10-1.08), the tapped density (F1-F9)(0.501-0.482), and the bulk density (F1-F9)(0.462-0.443) and also **Table 5** displays the ranges for the Carr's index (7.78–8.09), percentage porosity (11.3–36.5%), and angle of repose (43°79 ±0.1 – 31°79 ±0.2)

DSC Study

The DSC study provided valuable insights. It showed that the medication, polymers, and other excipients did not interact, which is a crucial finding for the stability of the drug formulation. The drug and drug-excipient physical combination (HPMC K15M, Sodium alginate) DSC spectra show that the peak location in the thermogram of the drug and drug-excipients did not significantly change. Figure 7 shows the single, endothermic peak that carbocysteine's differential scanning colorimeter thermogram displayed at 204°C, which correlates with the compound's melting transition temperature, and the HPMC K15M differential colorimeter showed a single, strong endothermic peak at 46.65°C. At 74.52°C, a second peak was observed. A major endothermic peak appears at about 100°C on the NaAlg DSC curve, whereas a sharp exothermic peak appears at 250°C. In the case of the optimized formulation, an endothermic peak was observed at 210°C, and other peaks were observed due to excipients. This lack of interaction further supports the stability of the drug formulation.

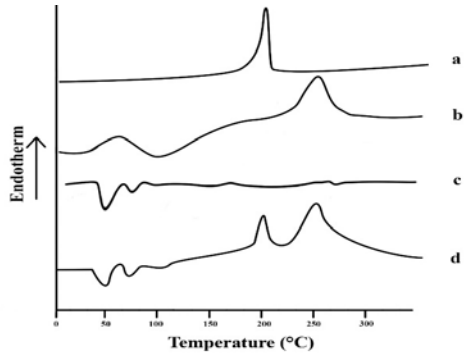

Figure 7: DSC thermogram of a) pure carbocisteine, b) sodium alginate, c) HPMC K15M, d) optimized formulation

Stability study

stability analysis of the enhanced recipe. The best formulation's stability experiments showed that when it was held at room temperature and 40^0C/75% RH, there were no appreciable changes in the physical properties. **Table 4** illustrates that no

appreciable alterations in physical attributes or percentage of drug release at 17 hours were noted throughout 3 months.

Table 4: Observation table of stability study

Parameters evaluated	Storage condition during stability study (40℃ ± 20C and 75% RH ± 5%)			
	0 days	30 days	60 days	90 days
Floating Study	17 hrs	17 hrs	17 hrs	17 hrs
% Drug content	99.45±0.19	99.23±0.36	98.86 ± 1.49	98.43 ± 0.56
% Drug release	98.16±0.79	97.82±0.8	97.73 ± 0.6	97.45 ± 0.5

Determination of drug entrapment efficiency.

With an increase in the drug-to-polymer ratio, the drug entrapment efficiency also increases. Formulation 1 had an alginate-to-drug ratio of 1:1 and an EE percentage of 80.12%. However, this was raised in F-2 to F-3, where **Figure 8** displays the observed %EE of optimized batch (F1-F3) and the Eudragit S 100 and HPMC K4M where displays the observed %EE of performed batches (F4-F9)

Scanning electron microscopy

The morphology of floating microspheres was investigated using scanning electron microscopy. **Figure 9** illustrates the observation of microspheres with a smooth surface shape and a hollow structure with fine pores. Microspheres have a porous inside surface and a smooth outside surface. It was studied to determine the morphology of floating microbeads.

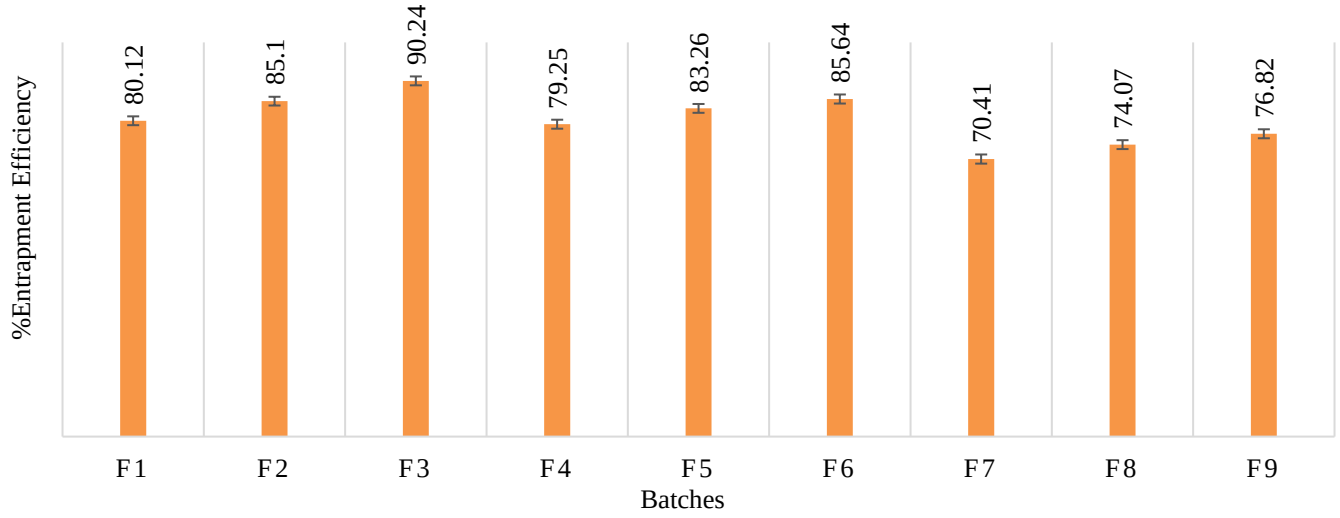

Figure 8: Entrapment efficiency of floating microbead batches

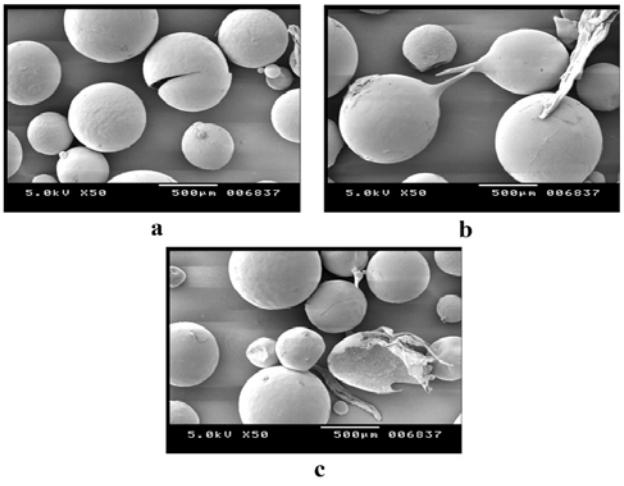

Figure 9: SEM images of floating microbeads containing (A) HPMC K4M (B) HPMC K15M optimized formulation (C) Eudragit S100

In vitro drug release study

Figure 10 shows the drug release for the formulations (F1-F9). The F1-F3 (HPMC K15M) formulation was determined to be the optimal formulation. Due to the creation of a porous and hollow structure, Formulation F3 exhibits improved floating ability for up to 17 hours. This allows the medicine to be delivered in simulated stomach juice via a gradual and continuous diffusion process. When particle size decreases, the rate at which drugs are released increases. HPMC K4M and Eudragit S100 exhibit reduced buoyancy over extended periods. Also, for formulations F4–F9, a smaller particle size indicates a lower release rate. In comparison to the two polymers, HPMC K4M and Eudragit S100, the cumulative percentage of drug release for the produced formulation after 17 hours in a sustained manner was discovered in the case of HPMC K15M. The diffusion-controlled release mechanism for the formulation followed first-order kinetics.

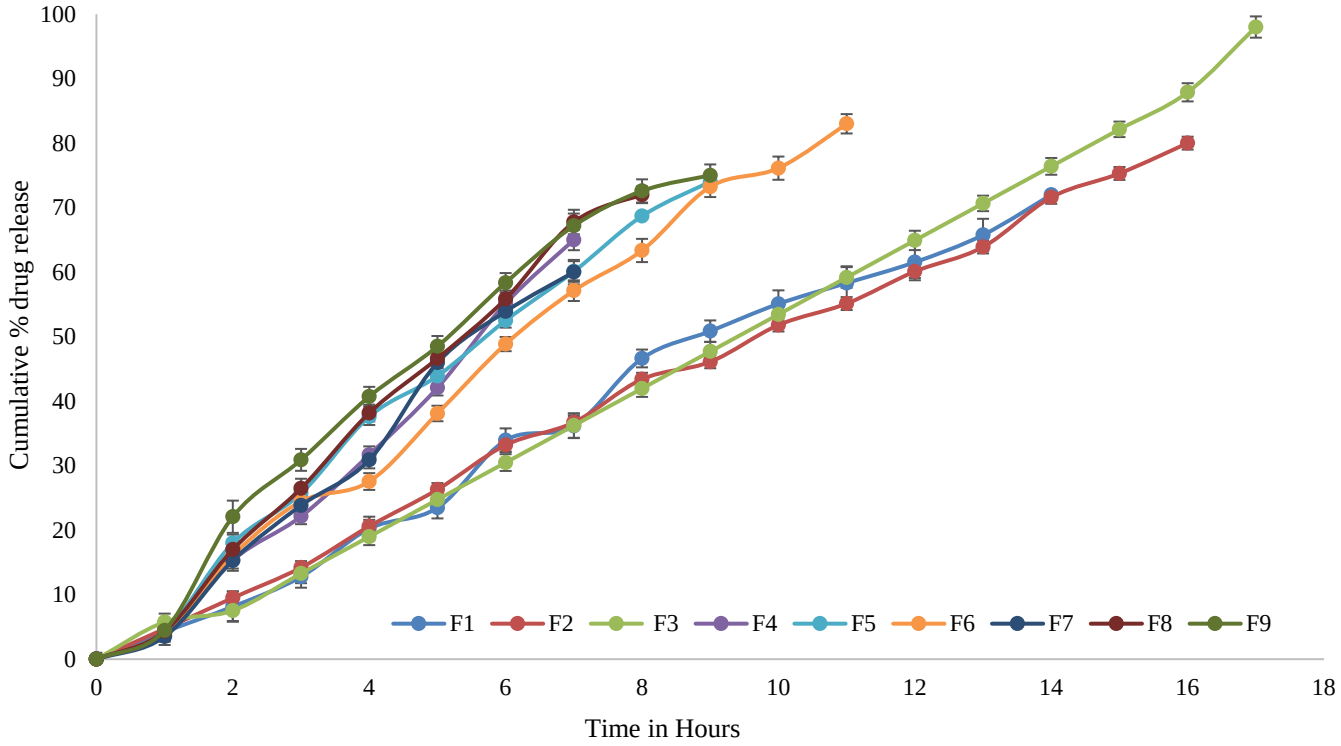

Figure 10: % drug release of formulation batches

Table 5: Evaluation observed of F1-F9 batches.

Evaluation parameters		F1	F2	F3	F4	F5	F6	F7	F8	F9
Physical appearance	Colour	White	White	White	White	White	White	White	White	White
	Appearance	Some are Oval and Round	Some are Oval and Round	Round	Some are Oval and Round	Some are Oval and Round	Round	Some are Oval and Round	Some are Oval and Round	Round
Particle size (µm)		240 ±0.5	240±0.8	245±00.2	268±00.6	275±0.8	286±0.9	311±0.7	325±0.4	332±0.2
Bulk density (gm/cm^3)		0.462±0.6	0.470±0.5	0.490±0.1	0.410±0.3	0.400±0.5	0.421±0.2	0.431±0.4	0.435±0.7	0.443±0.9
Tapped density (gm/cm^3)		0.501 ±0.5	0.516 ±0.4	0.540±0.2	0.480±0.3	0.465±0.5	0.452±0.9	0.438±0.8	0.472±0.6	0.482±0.4
Carr's index		7.78	8.91	9.25	12.29	13.97	6.85	1.59	7.83	8.09
Hausner's ratio		1.10	1.09	1.10	1.17	1.16	1.07	1.01	1.08	1.08
% porosity (%)		20.65	29.38	36.5	11.3	15.6	18.23	12.62	12.32	16.35
% Yield (%)		66.25	72.35	80.71	80.46	72.50	79.10	65.50	60.45	62.50
Angle of repose (θ)		39°65 ± 0.6	40°71± 0.4	43°79± 0.1	40°75± 0.6	42°64± 0.5	44°25± 0.7	39°75± 0.2	31°79± 0.4	34°72± 0.1
Drug content (%)		99.23 ± 0.19	99.40 ± 0.30	99.45 ± 0.36	94.35± 0.012	94.36± 0.15	95.52 ± 0.22	91.22± 0.15	92.31± 0.35	92.32± 0.52
Floating time (hr)		13	16	17	7	9	13	8	10	12

CONCLUSION

The current research demonstrates that the ionotropic gelation method is a simple, effective, and scalable method to prepare carbocysteine-loaded floating microbeads. The formulation batch F3 was optimized based on micropolitics, drug content, buoyancy time/ floating time, and drug release. The current

study successfully employed the modern concept of development, namely "quality by design," to identify control measures and systematically evaluate the manufacturing of Carbocisteine microbeads. The optimized batch F3 shows desired micrometric properties, drug content (99.40 ± 0.30 %), buoyancy time (17 hr), and drug release of 98.16 ± 0.79 % up to 17 hr. The prepared carbocystein-loaded microbeads effectively sustained the drug's release to improve absorption and achieve the desired therapeutic effect. A multiparticulate drug delivery system holds great potential for revolutionizing drug delivery and therapeutic strategies in upcoming years.

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CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Mayur Rambhau Gavit, Vaibhav L. Patil, and Nandini R. Mhatre conceived and designed the study and wrote the manuscript. They also conducted the research, contributed to data collection, and wrote the manuscript. Bhushan R. Rane and Ashish S. Jain have reviewed and edited the manuscript for clarity, grammar, and consistency.

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