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RESEARCH ARTICLE

Formulation of Natural Polymeric Floating In-Situ Gel for BCS Class II Drug Administration

Mr. Dhawal Dorwal[1], Dr. Aman Kansare[2], Dr. Sachin K. Jain[2] and Dr. Sudha Vengurlekar[2]
[1]Research Scholar, Faculty of Pharmacy, Oriental University, Indore (M.P.), India.
[2]Faculty of Pharmacy, Oriental University, Indore (M.P.), India.

*Corresponding Author
Mr. Dhawal Dorwal

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Abstract: The primary goal of this study was to develop an oral raft-forming in situ gel system for Albendazole (ABZ) that improves gastric retention, ensures controlled drug release, and maintains prolonged floating in the stomach. A two-factor, three-level (32) factorial design was used to formulate and optimize the in situ gel system. The study examined the effects of two independent variables—Gellan gum [A] and Carbopol 934 P [B]—on key responses, including floating lag time, percentage of water uptake at 2 hours, and drug release at 6 and 12 hours. The in vitro gelation study demonstrated rapid gel formation and prolonged retention. The results from the 32 factorial design showed that both factors significantly influenced the responses, confirming the accuracy of the optimization approach. Therefore, the developed oral raft-forming in situ gel system for ABZ presents a promising alternative for improving gastric retention and enabling sustained drug release by floating, ultimately enhancing the therapeutic efficacy of ABZ.

Keywords: In-situ gel, Gellan gum, albendazole, Floating, Carbopol 934P.

INTRODUCTION

Improved drug delivery and the creation of restricted substances have drawn more attention during the past three decades. Since in situ gel systems have shown benefits such ease of application, decreased frequency of use, and enhanced human pain compliance and comfort, their development has drawn a lot of attention in recent years.

Before being administered, gel dosage forms are liquid, but they become a gel that floats on the stomach when they come into touch with stomach contents. One or more mechanisms, including physiological cues (like temperature and pH), physical alterations in the biomaterial (like solvent transport and swelling), and grafts (like vaccinations), are responsible for this gel shift. Numerous production challenges affect the biodegradable polymers used to create in situ gels, In contrast to natural polymers, there are occasionally batch differences, explosive effects, non-reproducible drug release kinetics, operational problems, and the utilization of organic solvents. [1–2]

Albendazole is an unoriginal benzimidazole used to treat a variety of parasitic worm infections. It works well against roundworms, tapeworms, and flukes and is a broad-spectrum anti-helminthic.

It is used to treat a wide range of illnesses caused by parasitic worms, including neuro-cysticercosis, giardiasis, trichuriasis, and filariasis.[3]

Importance of in situ gelling system [4]

1. Its unique "Sol Gel transition" aids in the drug's regulated and prolonged release.
2. It aids in lowering the frequency of medicine delivery to the body.
3. A small dosage of the medication is needed, and there won't be any side effects or drug accumulation.
4. The medication will have a higher bioavailability.
5. The drug's residence period will be extended as a result of gel formation.

Advantages of in situ gel system[5-7]

1. Controlled and sustained release of the drug
2. Ease of the drug administration
3. It can be administered to unconscious patients
4. More patient compliance and comfort Minimizing the dose frequency and drug toxicity
5. Increased bioavailability

1.3 Disadvantages of in situ gel system[5-7]

1. It requires high level of fluids.
2. The sol form of the drug is more susceptible for degradation.
3. Chances of stability problems due to chemical degradation.
4. After placing the drug eating and drinking may become restricted up to few hours.
5. The quantity and homogeneity of drug loading into hydrogels may be limited, particularly for hydrophobic drugs.

Gellan gum

Gellan gum is a high molecular weight polysaccharide gum produced by a pure culture fermentation of a carbohydrate by strains of Pseudomonas elodea. This strain is also named now Sphingomonas elodea.Gellan gum is purified by recovery with ethanol or 2-propanol, dried and milled.The repeating unit of the polysaccharide

is a tetrasaccharide composed of two d-glucose units, one d-glucuronic acid residue and one of l-rhamnose residue and is substituted with acyl groups (glycerate and acetate groups as O-glycosidically linked esters). The glucuronic acid is neutralised to a mixed potassium, sodium, calcium and magnesium salt.gellan gum is an off-white powder which is soluble in water and insoluble in ethanol. In aqueous media, the substance produces thermoreversible gels when heated and cooled. The gelling behaviour is dependent on the acyl content, temperature and the presence of cations in the solution. While the native, non-deacylatedgellan gum forms soft and elastic gels, the deacylated gum forms firm and brittle gels. The addition of calcium, potassium, sodium and magnesium causes an increase of gel strength and brittleness. The gels are stable at temperatures up to 90°C and in a pH range between 3.5 and 8.

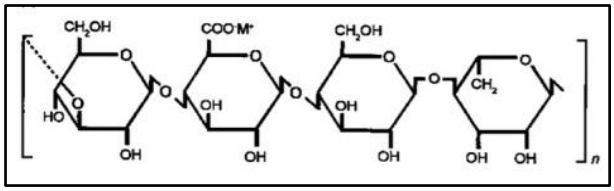

Fig. 1 Structure of Gellan Gum

Carbapol 934P

1. Carbopol 934P is a synthetic polymer used to make gels, emulsions, suspensions, and oral tablets. It's used in the pharmaceutical and cosmetic industries.
2. Uses
3. Formulating gels: Carbopol 934P can be used to make medium to high-viscosity gels.
4. Formulating emulsions: Carbopol 934P can be used to make emulsions.
5. Formulating suspensions: Carbopol 934P can be used to make suspensions.
6. Formulating oral tablets: Carbopol 934P can be used to make oral tablets.
7. Properties
8. Carbopol 934P is hydrophilic, biocompatible, and biodegradable.
9. Carbopol 934P has excellent swelling and thickening characteristics.
10. Carbopol 934P is mucoadhesive, which means it has an affinity for mucous membranes.
11. Composition
12. Carbopol 934P is made of acrylic acid and is crosslinked with allyl sucrose or allyl pentaerythritol.

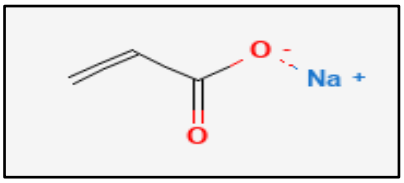

Fig. 2 Structure of Carbapol 934 P

METHODS

Drug Excipient Incompatibility Study

Physical observation of sample was done visually at every week for any change in the sample mixture foe 4 weeks.

The compatibility of drug and various excipients was studied by thin layer chromatography (TLC) technique. For study purpose, losartan potassium 10 mg was mixed thoroughly by mortar and pestle with excipient in ratio of 1:5 respectively and placed in tightly closed glass vials. All the vials were kept at 400c for 4 weeks. The samples were analyzed by physical observation and thin layer chromatography before and after storage.

Mobile phase preparation: for mobile phase, Methanol: Ammonia taken in the ratio of 70:30

Preparation of in-situ gel[11-13]

All the additives used in the preparations were passed from a No. 60 sieve (250 microns). Required ingredients for the preparation, like Gellan gum, Carbapol 934 P, sodiumbicarbonate, and sodium citrate, were accurately weighted as per the formulation chartdepicted in Table 2.Carbapol 934 Pwas dissolved using 40 mL of deionized water.Therequired quantity of sodium bicarbonate and sodium citrate were incorporated in it whilestirring to attain complete homogenous dispersion. 30 mg Albendazole drug was dissolved in the solution.Gellan gumwas dissolvedusing deionized water (30 mL) taken in a beaker pre-heated to around 60 ◦C on a hot platewith continuous stirring. The Gellan gumsolution was cooled to 40 ◦C and

added to the Carbapol 934 P solution. The total amount ofthepreparationfinallyreached100mL, makinguseofdistilledwaterafteraddingmethylparabenasapreservativeandmixedthoroughly.

32 factorial design for the oral raft-forming in situ gelling system of Albendazole, obtained using Design-Expert software (version 130.2.0) from Stat-Ease Inc., Minneapolis, MN, USA.[1]

Table 1 Formulation of in-situ gel

S.No.	Ingredients	Quantity taken								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Albendazole (mg)	30	30	30	30	30	30	30	30	30
2	Gellan gum (g)	1	2	3	1	2	3	1	2	3
3	Carbopol 934 P (g)	1	1	1	1.5	1.5	1.5	2	2	2
4	Calcium carbonate (mg)	50	50	50	50	50	50	50	50	50
5	Sodium bicarbonate (mg)	50	50	50	50	50	50	50	50	50
6	Sodium citrate (mg)	25	25	25	25	25	25	25	25	25
7	Methyl paraben (mg)	10	10	10	10	10	10	10	10	10

Experimental Design[01]

The interaction and relationship between dependent and independent variables can be studied using a scientific and systemic approach, i.e., experimental design. The optimization of the formulations was performed using 32 factorial design. The effect of the independent variables and their interactions can be determined from the chosen experimental design, which can provide a satisfactory degree of freedom. Two independent factors (variables), Gellan gum (A) and Carbapol 934 P (B), were selected and evaluated at two levels, i.e., higher level (1), medium level (0), and lower level (+1). The responses (independent variables) chosen to know the effect of the factors were floating lag time, % water uptake at 2 h, and % drug release at 6 h and 12 h. The analysis of the obtained data was carried out employing Design-Expert software (version 130.2.0) offered from Stat-Ease Inc., Minneapolis, MN, USA. Table 3 enlist the factors and their levels for preparing the oral raft-forming in situ gelling system of Albendazole

Table 2Composition of independent variables and their levels for the preparation of the oral raft-forming in situ gelling system of Albendazole

Variables	Actual value (g)			Code value		
	Low	Medium	High	Low	Medium	High
Gellan gum	1	2	3	-1	0	1
Carbapol 934 P	1	1.5	2	-1	0	1

Evaluation

Physicochemical properties

The colour, odour and taste of the formulated in-situ gel of albendazolewere determined as per the senses.[13]

Determination of drug content

Accurately, 10 ml of the formulation (containing the equivalent of 30 mg albendazole) from different batches was measured and transferred to 100 ml volumetric flasks. To this 50-70 ml of 0.1 N HCl was added and sonicated for 30 min. Volume was adjusted to 100 ml. Complete dispersion of the contents was ensured visually and the dispersion was filtered using Whatman's filter paper. From this solution, 10 ml of sample was withdrawn and diluted to 100 ml with 0.1N HCl. Contents of albendazolewere measured at a maximum absorbance at 235 nm using UV-Visible spectrophotometer.[14]

pH measurement

pH of the prepared formulations was measured using a calibrated digital pH meter at 27 ˚C [6].

In vitro gelation study

To evaluate the formulation for their in vitro gelling capacity accurately measured 1 ml of the colored formulation were added to 5 ml of the gelation solution (0.1 N HCl, pH 1.2) at 37 ˚Cin a test tube with mild agitation that avoids breaking of formed gel. The in vitro gelling capacity was graded in three categories on the basis of the stiffness of the formed gel, gelation time and time period for which they formed gel remains as such (+) gels after few minutes, dispersed rapidly; (++) gelation immediate remains for few h; (+++) gelation immediate remains for an extended period.[15-17]

In vitro floating study
The in vitro floating study was carried out by introducing 10 ml of the formulation into a beaker containing 900 ml of 0.1 N HCl (pH 1.2) at 37 ˚C without much disturbance. The time the formulation took to emerge on the medium surface (floating lag time) and the time the formulation constantly floated on the surface of the dissolution medium (Duration of floating) were recorded.[19]

Measurement of water uptake
The water uptake by the gel of selected formulation of sodium alginate was determined by a simple method. In this study, the in- situ gel formed in 40 ml of 0.1 N HCl (pH 1.2) was used for each formulation the gel portion from the 0.1N HCl was separated, and the excess HCl solution was blotted out with a tissue paper. The initial weight of the gel taken was weighed, and to this gel, 10 ml of distilled water was added and after every 30 min of the interval water was decanted and the weight of the gel was recorded and the difference in the weight was calculated.[18]

Viscosity
The formulation should have an optimum viscosity that will allow ease of administration and swallowing as a liquid and produce satisfactory gel strength for use as a delivery vehicle. Results of viscosity for formulationsare shown in table. The formulations showed an increase in viscosity with increasing the concentration of gel forming polymer sodium alginate as a consequence of the increase in chain interaction. The concentration of sodium alginate (250 mg and 300 mg) was found to produce a satisfactory viscosity increase which provides sustained release of the drug. Calcium carbonate also contributes to increasing the viscosity of the formulations.

Measurement of gel strength
A sample of 50g of the gel formed in 0.1 N HCl (pH 1.2) was introduced into a 100ml graduated cylinder. A weight of 35g was placed onto the center of the surface of the gel and allowed to penetrate through the gel. The time taken by the 35 g weight to penetrate 5 cm down through the gel was noted for all formulations. The same procedures were followed for each fresh formulation in triplicate and average time was determined

Swelling index
The gel swelling index of the selected formulation is determined by a simple method. In this study, an in-situ gel formed in 40 ml of 0.1NHCl(pH1.2)wasused.Separatethe0.1NHClgelfractionfromeach formulation, and remove the excess HCl solution with papertowels.Weightheinitialweightofthegel,add50mlofdistilledwa-tertothegel,pouroutthewaterafter12hours,recordtheweightof the gel, calculate and report the weight difference

In vitro drug release study
The dissolution studies were performed in triplicate using type I (basket method) dissolution apparatus. The dissolution medium used was 900 ml of 0.1 N HCl maintained at 37 ˚C. The stirring rate was adjusted to 50 rpm. This speed was believed to stimulate the in vivo existing mild agitation and was slow enough to avoid the breaking of gelled formulation. At predetermined time intervals 1 ml samples were withdrawn and replaced by fresh dissolution medium, filtered through what Mann's filter paper, diluted and assayed at a maximum absorbance at 235 nm using double beam UV-Visible spectrophotometer.[20]

Kinetics of Drug Release Studies
To determine the kinetics of the drug release, the dissolution profile of each batch was adapted for different models, including first-order, zero-order, Hixon and Crowell, Higuchi, and KorsemeyerPeppas (KP). The KP equation describes the method to explain the drug release mechanisms

9. In vivo study[21]
The animal experiment was carried out in compliance with the protocol of the Institutional animal ethical committee (IAEC: 1877/PO/Re/S/16/CCSEA/2024/021).
Six White rabbits with mean weight of 2.5 ± 0.3 kg were used. The rabbits were accommodated to the dosing for 1 month before the study to prevent withdrawal and defense reaction that may lead to inac- curate dosing. The rabbits were kept in a single cage and fasted for 12 h before the study with free access to water during the experiments. A cannula was inserted into the marginal ear vein for blood sampling and flushed with heparinized normal saline solution.

Study design- [21]
White rabbits were selected as an experimental model because they provide a well controlled animal model for screening the oral absorption potential of oral formulations. In a cross-over study with 1 week apart as a wash out period,l gm oral in situ gel ABZ (equivalent to 10 mg ABZ) was deposited in oral cavity. The animals also received 5 ml of oral drug solution ABZ SO (equivalent to 10 mg ABZ).
Sample preparation:[21]

Blood samples were centrifuged and the plasma was separated from the cells. All plasma samples were stored at –20 Absolute Eosinophil Count (AEC) until analysis. Plasma was extracted by placing 200 IL of plasma sample in a glass tube. Sodium metabisulphite (100 ÌL) and 2 ml of ethyl acetate were added. Tube was vortexed for 10 min and then placed on a shaker, shaking gently for another 20 min. After centrifugation at 2000 rpm for 10 min, 2 ml of the organic layer of tube was removed, placed in a new labelled 12x75 mm glass tube and evaporated in a Thermo Savant rotary vacuum chamber and Refrigerated The residue was re-suspended in 200 ÌL of methanol for HPLC analysis. Before analyzing plasma samples, ABZ and ABZ-SO standard solutions prepared in methanol were run on HPLC to optimize analysis and standardize calibration. Standard drug and metabolite concentrations were chosen on the basis of levels found in plasma samples. ABZ standard solutions used were in the range of 0.05 to 0.4 Ìg/ml while those for ABZ-SO was 0.5 to 25 Ìg/ml.

HPLC analysis-[21]

The HPLC system consisted of a CMB Controller,Pump, Auto Sampler, Degasser and a Fluorescence Detector set at Ex 280 nm,. A reverse-phase, Luna 5-Ìm C18 (2) column, 250x4.6 mm was used with a Shimadzu Column Oven set at 45AEC. The mobile phase was a mixture of 0.01M phosphoric acid in deionized water and acetonitrile (80:20 v/v) containing 5 M tetra-butyl-ammonium hydrogen sulfate, pH 2.2. The sample injection was 10 ÌL. The flow rate was set at 1.0 ml/min and the run time for each sample was 20 min. All data were recorded and analysed on a computer with Class-vp Chromatography Data System Software. Plasma ABZ and ABZ-SO concentrations were determined by reference to corresponding standard curves, calculating the mass of samples, multiplying with appropriate dilution and recovery factors.

Statistical analysis-

All statistics were performed using GraphPad In Stat on Prism The Student's t-test was used to compare the data of two groups. A p-value of less than 0.05 was considered to represent a statistically significant difference. All values are presented as mean±SE.

Stability Study as per ICH guidelines:[12-14]

The optimized formulation ABZ was initially stored in glass bottles and subjected to a three-month stability study. Subsequently, the in-situ gels were monitored for stability over a period of 6 months under accelerated conditions. At regular intervals of 0, 3 and 6 months, samples were taken from the stored formulations and assessed for appearance, drug content, floating study, viscosity and percentage drug release.

The stability testing of the optimized formulation was carried out in accordance with the International Council for Harmonisation (ICH) guidelines. Long-term stability conditions were maintained at 30±2°C/65±5% relative humidity (RH), while accelerated stability conditions were set at 40±2°C/75±5% RH for at least 6 months. The evaluation of the product stability focused on observing any significant changes during the study period.

The stability studies were conducted using stability chambers. Samples were withdrawn at designated time intervals of initial, 3, and 6 months for further evaluation. Stability data covering a minimum of 6 months was considered sufficient for long-term studies, provided no significant changes were observed under the accelerated conditions.

Physical appearance:

The initial physical appearance of the optimized formulation was observed and subsequently, at 0, 3 and 6-month intervals. Throughout this three-month period, the optimized formulation maintained its excellent physical appearance, with no observable color changes or alterations.

Drug content %: The drug content percentage of the test formulation was assessed at specific time intervals, namely 0 month, 3 months and 6 months. For each collected sample, the drug content percentage of the optimized formulation was determined. The obtained results were then compared to the acceptance criteria for Albendazole drug assay as per the IP specification limit, which falls within the range of 90.0% to 110%. % of Drug release:[12-14]

The drug release study of the in-situ gel containing 80 mg of Albendazolewas conducted using the USP type II paddle type apparatus at 37 ± 0.5ºC and 50 rpm. The dissolution medium used was 900 ml of 0.1 N HCl (pH 1.2). A 10 ml volume of the in-situ gel was used for the test. At predetermined time intervals, a sample solution of 5 ml was withdrawn from the dissolution medium. The withdrawn samples were then filtered through a 0.45 µm membrane filter, suitably diluted and analyzed using UV spectrophotometric 280 nm. To maintain a sink condition, fresh dissolution medium was replaced immediately after withdrawal of each test sample. The dissolution studies were carried out for a total duration of 12 hours. The test formulation's drug release percentage was determined at different specified time intervals.

Long term stability studies:[12-14]

The results of the long term stability studies of the optimized formulation ABZ, conducted under conditions of 30±2°C/65±5%RH, are presented in Table

Physical Appearance:
Throughout the 6-month stability period, there were no observable changes in the physical appearance of the optimized formulation. The in-situ gel maintained its original color without any discoloration.

b. % Drug Content:
The drug content of the optimized formulation was found to be highly consistent over the 6-month period. At the start of the study (0 month), the drug content was determined to be 99.94±0.21%. Subsequent testing at 3 months and 6 months showed minor variations, with drug contents of 99.37±0.18% and 99.15±0.03%, respectively. These results indicate that the optimized formulation remained stable with minimal drug degradation or loss during the storage period.

c. Floating Time:[12-14]
The floating time of the optimized formulation also remained constant throughout the 6-month stability study. The in-situ gel consistently exhibited a floating time of 12 hours at each time point (0 month, 3 months, and 6 months). This demonstrates that the buoyancy of the formulation was retained, ensuring prolonged residence time in the stomach for sustained drug release.

d. Viscosity:
The viscosity of the optimized formulation remained relatively stable during the long term stability study. There were minimal changes in viscosity values over the 6-month period, with recorded values of 443±0.10, 442±0.15, and 441±0.20 cps at 0 month, 3 months and 6 months, respectively. This suggests that the rheological properties of the in-situ gel were well-preserved throughout the storage period.

e. Gel Strength:[12-14]
The gel strength of the optimized formulation was consistently maintained during the 6-month stability study. The recorded gel strength values were 10.82±0.12 N/m2 at 0 month, 10.78±0.15 N/m2 at 3 months and 10.73±0.17 N/m2 at 6 months. These results indicate that the gel maintained its structural integrity and mechanical strength during the storage period.
Overall, the long term stability study data for the optimized formulation ABZ suggest that the in-situ gel remains stable and preserves its physical appearance, drug content, floating behavior, viscosity and gel strength over a period of 6 months under the specified storage conditions. These findings are encouraging and support the potential of the optimized formulation for future applications as an effective and stable drug delivery system.

Accelerated stability studies:[12-14]
The results of the accelerated stability studies of the optimized formulation ABZ, conducted under conditions of 40±2°C/75±5%RH, are presented in Table.

Physical Appearance:
Similar to the long term stability results, the physical appearance of the optimized formulation remained unchanged throughout the 6- month accelerated stability study. There were no observable colour changes or any other visual alterations, indicating the preservation of the formulation's integrity and stability.

b. % Drug Content:
The drug content of the optimized formulation showed good stability during the accelerated stability study. At the beginning of the study (0 month), the drug content was measured to be 99.94±0.01%. At 3 months and 6 months, the drug content slightly decreased, with values of 99.14±0.07% and 99.03±0.21%, respectively. Although there were minor variations, the drug content remained within an acceptable range, demonstrating the formulations ability to maintain drug integrity over the accelerated storage period.

c. Floating Time: [12-14]
The floating time of the optimized formulation was consistent during the accelerated stability study. The in-situ gel exhibited a constant floating time of 12 hours at each time point (0 month, 3 months and 6 months). This suggests that the buoyancy of the formulation was retained, ensuring its prolonged gastric retention and sustained drug release behavior.

d. Viscosity:
The viscosity of the optimized formulation also showed good stability over the 6-month accelerated stability study. There were negligible changes in viscosity values, with recorded values of 413±0.10 cps at 0 month, 421±0.28 cps at 3 months and 410±0.36 cps at 6 months. This indicates that the rheological properties of the in-situ gel were well-maintained under accelerated conditions.

e. Gel Strength:

The gel strength of the optimized formulation remained constant during the accelerated stability study. The measured gel strength values were 08.82±0.12 N/m2 at 0 month, 08.75±0.23 N/m2 at 3 months and 08.68±0.28 N/m2 at 6 months. These results indicate that the gel retained its structural integrity and mechanical strength even under the accelerated storage conditions.

Overall, the accelerated stability study data for the optimized formulation ABZ demonstrate its ability to maintain physical appearance, drug content, floating behavior, viscosity and gel strength over the 6-month storage period under accelerated conditions of elevated temperature and humidity. These findings reinforce the stability and robustness of the optimized formulation and provide valuable insights for its potential application as a reliable and effective drug delivery system

In vitro drug release:
The results of % drug release for the ABZ formulation under both long term (30±2°C/65±5% RH) and accelerated (40±2°C/75±5% RH) stability conditions at 0, 3, and 6 months are presented in Table and figures

Under Long Term Stability (30±2°C/65±5% RH):
The % drug release from the ABZ formulation at each time point (0, 3, and 6 months) remained consistent. At the initial time point (0 months), the % drug release was 0% as expected, as no release occurred immediately after preparation. As the time progressed, the drug release increased, reaching 99.85±0.09% at 12 hours, which indicates the complete release of the drug from the formulation. There were minor variations in drug release values at 3 and 6 months (ranging from 99.83±0.28% to 99.82±0.12%), but overall, the formulation exhibited a sustained and stable drug release profile.
b. Under Accelerated Stability (40±2°C/75±5% RH):

Similar to the long term stability results, the % drug release from the ABZ formulation at accelerated conditions showed consistency. At 0 month, the drug release was indicating no immediate release upon preparation. The drug release increased with time and at 12 hours, the % drug release reached 99.85±0.09%. Throughout the 3-month and 6-month time points, the drug release values showed minor fluctuations but remained within the range of 99.81±0.09% to 99.80±0.09%, demonstrating the maintenance of drug release performance under accelerated stability conditions.

Overall, the ABZ formulation demonstrated a stable and sustained drug release profile both under long term and accelerated stability conditions. The similarity in drug release profiles between the two stability conditions indicates the formulation's robustness and its ability to maintain drug release behavior under different storage conditions. These results are promising and suggest that the ABZ formulation has the potential for successful application as an effective and reliable drug delivery system

RESULTS AND DISCUSSION

8. Drug excipient incompatibility study

Table 3 Drug excipient incompatibility study

S. No.	Parameter	Initial	After 4 week	Observation
1	Albendazole (Pure Drug)	White	No change	No change
2	Drug + Carbapol 934 P	White	No change	No change
3	Drug + Gellan gum	White	No change	No change
4	Drug + Calcium carbonate	White	No change	No change
5	Drug + Sodium bicarbonate	White	No change	No change
6	Drug + Sodium citrate	White	No change	No change
7	Drug + Methyl paraben	White	No change	No change

Agent. In addition sodium, bicarbonate was also included in the formulations as an additional gas generating agent to enhance floating behaviour of the In situ gelling system of albendazole.

Physicochemical properties
The formulated oral In situ gelling system of albendazolewas found to be off white in colour with characteristic odour and a bland taste.

Drug content
The percentage drug content for all formulation was determined and shown in table 3. The drug content was found to be in the range of 94-98% for all the formulations indicating a uniform distribution of the drug.

pH measurement

The measurement of pH is very important for oral preparations. Otherwise, it leads to irritation to the throat. All the formulations had a slightly alkaline pH. The pH of formulations was found in the range of 7.1- 7.8 as shown in table 4

Table4 Evaluation parameters of the oral raft-forming in situ gelling system of ABZ

Formulations	pH	Drug Content %	In Vitro Gelation	Floating Lag Time * (min)	Total Floating Time (h)	Water Uptake at 2h*%	% Drug Release * (6 h)	% Drug Release * (12 h)
F1	7.5 ± 0.21	94.6 ± 0.38	+++	3.12 ± 0.5	>20	40 ± 0.52	70.1 ± 0.35	98.56 ± 0.15
F2	7.4 ± 0.42	95.6 ± 0.32	+++	2.35 ± 0.6	>10	4.9 ± 0.52	63.5 ± 0.23	85.26 ± 0.23
F3	7.3 ± 0.34	95.0 ± 0.41	+++	5.58 ± 0.6	>10	38 ± 0.61	55.6 ± 0.23	80.56 ± 0.13
F4	7.8 ± 0.35	94.3 ± 0.12	+++	28± 0.5	2	10 ± 0.28	68.2 ± 0.25	82.56 ± 0.47
F5	7.5 ± 0.26	94.8 ± 0.34	+++	40 ± 0.6	>09	20.3 ± 0.22	43.6 ± 0.52	70.54 ± 0.56
F6	7.2 ± 0.21	98.5 ± 0.31	+++	47 ± 0.3	>10	18.7 ± 0.39	30.2 ± 0.25	52.44 ± 0.87
F7	7.5 ± 0.36	95.4 ± 0.26	+++	70 ± 0.2	<4	08.53 ± 0.23	40.3 ± 0.09	65.21 ± 0.58
F8	7.1 ± 0.29	97.2 ± 0.11	+++	82 ± 0.8	<4	28.52 ± 0.21	30.5 ± 0.23	55.16 ± 0.22
F9	7.5 ± 0.25	95.7 ± 0.52	+++	87 ± 0.5	<3	9.5 ± 0.11	25.4 ± 0.52	53.73 ± 0.56

Mean±SD,n=3.
+++ Indicates good In vitro gelation capacity

Table 5 Evaluation parameters of the oral raft-forming in situ gelling system of ABZ

Formulations	Gel Strength(Sec)	Viscosity (Cps)	Swelling Index(%)
F1	18.32 ± 1.50	220	26.15 ± 1.60
F2	23.62 ±1.55	250	41.50 ± 1.15
F3	28.45 ± 1.56	280	72.34 ± 1.25
F4	30.56 ± 1.20	356	35.60 ± 1.36
F5	45.54 ±0.49	405	45.10 ± 2.31
F6	43.14 ±1.21	465	65.12 ± 0.65
F7	53.20 ± 137	390	22.56 ± 1.20
F8	56.55 ± 1.23	490	48.12 ± 2.20
F9	69.35 ± 1.25	570	81.50 ± 2.15

In vitro gelation study

All the prepared formulations resulted in immediate gelation that was retained for an extended period. The systems that resulted in instantaneous gel formation upon exposure to biological fluids and body temperature are ideal in situ gelling systems. As the concentration of Carbapol 934 P increased, gelation was observed to be enhanced. Formulations with the lowest concentration of polymer resulted in weak gel formation, which may not be able to withstand peristaltic waves of the GIT. Hence, an optimum polymer concentration was required to get an ideal gelling system.

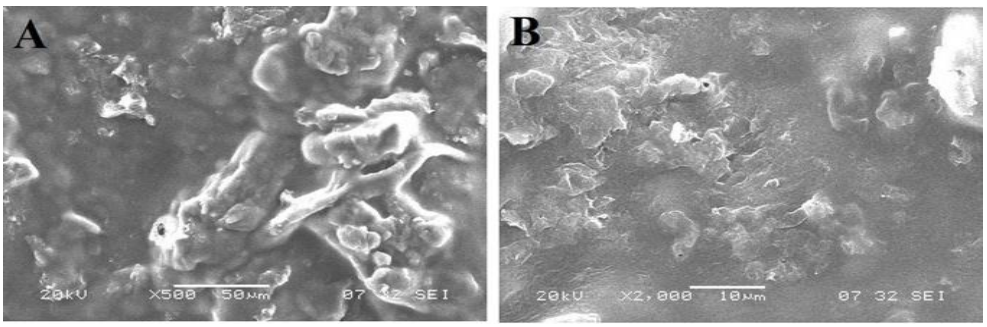

Fig. 3 Scanning electron micrographs of (A) ABZ (pure drug) at 500× magnification and (B) ABZ Gel at 2000× magnification

In vitro floating study

When the system is buoyant, drug can be released at a desired rate and, in turn, diminish the side effects of the drug, such as gastric ulceration, by avoiding direct contact with the stomach mucosa. The time required by the system to float on the surface of the medium is termed floating lag time, which is the preliminary measure of the floating performance of the

formulation. The duration of floating is the total period of floating of the formulation on the surface of the medium. In vitro floating is an obligatory parameter to be assessed prior to the assessment of the formulation in vivo. From our previously published study, it was observed that the excess concentration of sodium bicarbonate that has been incorporated as a gas-forming agent to achieve buoyancy decreased the floating lag time and floating duration of the formulations. In the present study, the previously optimized concentration of sodium bicarbonate (1%) was used along with sodium citrate (1%), which was used to maintain fluidity of the formulation prior to administration. Gellan gum and Carbapol 934 Pwere used as gelling agents. All the developed formulations were shown to float on the surface of 0.1N HCL (simulated gastric fluid), but formulations with a higher concentration of Carbapol 934 P (F4–F9) showed a floating lag time of more than 30 min and the formulations F1, F2, and F3 showed a floating lag time of 2.4, 3.1, and 6.2 min, respectively. The results of floating duration were different for all the formulations. Formulation F1 remained floating for more than 24 h, whereas F2, F3, F5, and F6 remained buoyant for less than 12 h. The floating duration of formulations F7 to F9 was less than 3 h, which may have been due to the higher concentration of Carbapol 934 P. F4 showed a floating duration of just 1 h, after which the gel formed was settled at the bottom. Hence, it can be concluded from the results of the floating study that formulations with a higher Carbapol 934 P concentration are not be an ideal composition for an in situ gelling system. Among all the formulations, F1, F2, and F3 exhibited desirable floating on the surface of the medium.
Measurement of water uptake by the gel

The formulation exhibited water uptake which is observed in the range of 10-107% as shown in table 4. The release of the drug from the polymer matrix depends on the amount of water associated with the system. The release of the drug may involve the penetration of the water into the matrix and simultaneously release the drug via diffusion or dissolution. The water associated with the formulation at any point in the time can be determined by the simple test for all the formulation of Gellan gumbased in- situ gel of ABZ. From the study, it was concluded that formulation F5 Containing 250mg and F6 containing 300 mg of the Gellan gumresulted in 100% water uptake, in turn, a good release of the drug from the polymer.

In vitro drug release study

A combination of different polymer (Carbapol 934 P and Gellan gum) concentrations was used to sustain the drug release from the prepared in situ gel formulations. In vitro drug release profile studies were performed on all formulations (F1–F9), as shown in Figure 4. All prepared formulations showed a sustained drug release. F1 (% Carbapol 934 P andGellan gum1:1) showed nearly 100% drug release, and F2, F3, and F4, showed nearly 83% drug release at 12 h. The in vitro drug release study revealed that as the polymer concentration increased there was a considerable decrease in the rate and extent of drug released from the formulation, which was due to an increase in the density of the polymer matrix as well as an increase in the diffusional path length of the drug molecules. F9 showed the least drug release, at 48.73% at 12 h; this was due to the high concentration of both polymers, which formed thick sol–gel formations that retarded the drug release from the formulation. F5, F6, F7, and F8 showed 72.31%, 53.44%, 67.91%, and 57.16% drug release at 12 h, respectively. In all in situ gel formulations, the slow diminution of gel matrix and thickness throughout the in vitro drug release study was due to gel erosion. Polymer gel erosion caused gradual decreases in gel matrix thickness and in all in situ gel formulations throughout the drug investigations. It was seen throughout the experiment that the gel matrix in the dissolution medium quickly swelled at 6–8 h, followed by an erosion of the gel matrix polymer after 10 or 12 h. F1 showed continuous floating for 24 h and sustained the drug release for up to 12 h; hence, it was chosen as the optimized formulation

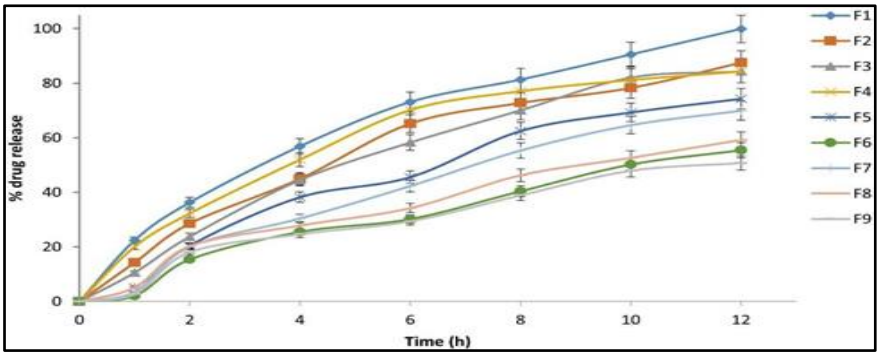

Fig. 4In vitro drug release profile of the oral raft-forming in situ gelling systems of Albendazole viz. formulations (F1–F9).

Kinetics of Drug Release Studies

According to the regression coefficients, the kinetics of the dissolution data were well suited to the zero-order, Higuchi matrix, Hix Crow, and KP models (KP) (Table 6). Diffusion, swelling, and erosion were the three most essential rate-control mechanisms for the controlled release formulations. The swelling formulations and diffusion mechanisms comprised the relaxing of polymer chains and water absorption, leading the polymer to swell from glassy to rubbery. The mechanism of drug release from the formulation is indicated by the diffusion exponent n. In the KP equation, if the n value is below0.43

it indicates the release of Fickian diffusion, and if the n value is between 0.43 and 0.89 it indicates non-Fickian (anomalous) transport; n values above 0.89 indicate a case II transport mechanism. This KP model is used to examine drug release from dosage forms when there is more than one type of drug release mechanism or when the release mechanism is unknown. For all factorial design formulations, the value of the diffusion exponent n was between 0.365 to 0.752. The formulations F3, F5, F6, F8, and F9 were found to have non-Fickian release, whereas F1, F2, F4, and F7 were found to have Fickian release. F2, F2, F4, F5, F7, and F8 were best suited to Peppas release, and F6 and F9 were found to be Hix Crow models, respectively. However, F1 showed zero-order release and F3 showed matrix release, as shown in Table 5. The optimized formulation F1 showed Fickian diffusion with zero-order drug release.

Table 6Kinetic studies of the dissolution profile of NTB matrix tablets (values of R2, k, and n) and mechanism of drug release.

Formulation	Zero Order		Hix Crow		Higuchi Matrix		1st Order		Korsmeyer–Peppas			Mechanism of Release	Drug Releas Kinetics
	R2	K	R2	K	R2	K	R2	K	R2	K	n		
F1	0.994	8.225	0.968	23.53	0.979	11.26	0.971	9.562	0.982	8.563	0.255	fickian	Zero order
F2	0.918	7.532	0.973	13.42	0.871	15.24	0.945	9.065	0.996	10.542	0.247	fickian	Peppas release
F3	0.974	4.135	0.835	8.521	0.997	17.26	0.994	14.562	0.987	16.254	0.364	Nonfickian	Higuchi matrix
F4	0.942	10.456	0.899	9.245	0.934	9.256	0.992	8.635	0.995	12.654	0.199	fickian	Peppas release
F5	0.891	8.548	0.971	8.654	0.909	14.24	0.919	10.254	0.979	10.235	0.472	Nonfickian	Peppas release
F6	0.917	13.562	0.993	15.24	0.781	15.24	0.984	9.524	0.843	19.547	0.485	Nonfickian	Hix Crow
F7	0.932	11.256	0.789	8.652	0.927	19.26	0.912	8.541	0.998	14.547	0.191	fickian	Peppas release
F8	0.874	15.245	0.985	11.24	0.801	8.265	0.951	11.254	0.992	8.654	0.572	Nonfickian	Peppas release
F9	0.909	8.324	0.987	9.256	0.923	9.236	0.926	9.487	0.975	13.256	0.366	Nonfickian	Hix Crow

Mean±SD,n=3.

Data Analysis and Optimization

The effect of independent variables such as the concentration of Gellan gum(A) and Carbapol 934 P (B) on responses such as floating lag time, percentage water uptake, and percentage drug release was analyzed using 32 factorial designs. When different concentrations of factors were loaded at three levels (high, medium, and low), nine different formulations were obtained from the software. The formulations and their responses are depicted in Table.

Table 7 Observed responses in 32 full factorial design for the oral raft-forming in situ gelling system of ABZ

Formulations	Variables		Responses			
	A (Gellan gum) g	B (Carbapol 934 P) g	Floating Lag Time * (min)	Water Uptake at 2 h * (%)	% Drug Release * (6 h)	% Drug Release * (12
F1	1	1	3.12 ± 0.5	40 ± 0.52	70.1 ± 0.35	98.56 ± 0.15
F2	2	1	2.35 ± 0.6	4.9 ± 0.52	63.5 ± 0.23	85.26 ± 0.23
F3	3	1	5.58 ± 0.6	38 ± 0.61	55.6 ± 0.23	80.56 ± 0.13
F4	1	1.5	28± 0.5	10 ± 0.28	68.2 ± 0.25	82.56 ± 0.47
F5	2	1.5	40 ± 0.6	20.3 ± 0.22	43.6 ± 0.52	70.54 ± 0.56
F6	3	1.5	47 ± 0.3	18.7 ± 0.39	30.2 ± 0.25	52.44 ± 0.87
F7	1	2	70 ± 0.2	08.53 ± 0.23	40.3 ± 0.09	65.21 ± 0.58
F8	2	2	82 ± 0.8	28.52 ± 0.21	30.5 ± 0.23	55.16 ± 0.22
F9	3	2	87 ± 0.5	9.5 ± 0.11	25.4 ± 0.52	53.73 ± 0.56

***Mean±SD,n=3.**

The obtained results show that the independent variables had a significant impact on the dependent variables selected, such as floating lag time (ranging from 2.4 to 87 min), percentage water uptake (ranging from 4.9 ± 0.52 to 40 ± 0.52 %), and percentage drug release (ranging from 25.4 ± 0.52% to 98.56 ± 0.15%). For given levels of each independent variable, the equation in terms of coded factors can be utilized to made predictions about the response. The high levels of the factors are coded as +1 and the low levels of the factors are coded as −1 by default. By comparing the factor coefficients, the coded

equation can be used to determine the relative impact of the components. A positive value in the factorial equation indicates a direct relationship with the independent variable. The particular response and a negative value denote inverse correlation between independent variables, and the response is depicted in Table.

Table 8 Multiple regression output for dependent variables, showing the intercept, relationship between the factor and variables, and p-value obtained from the software.

	Intercept	A[1]	A[2]	B[1]	B[2] R2
Floating lag time	40.4259	−4.93564	1.4523	−36.4486	−1.07896 0.9924
p−value		0.033	0.033	<0.0001	<00001
% Water uptake at 2 h	18.6544	-1.76142	−1.5423	8.0459	−53511 0.9111
p−value		0.038	0.039	0.0314	0.0517
% Drug release at 6 h	47.0256	−1.09	10.01	1.54	4.6808977
p−value		0.0245	0.0542	0.0254	0.0197
% Drug release at 12 h	71.256	−1.10	8.564	2.65	+3.05 0.9312
p−value		0.0452	0.0351	0.0452	0.0528

Impact of Independent Variables on Floating Lag Time Response

Formulations F1, F4, and F7, with the same concentration of sodium alginate but different concentrations of Carbapol 934 P, showed a variation in floating lag time. It was observed that as the concentration of Carbapol 934 P increased, floating lag time also increased. The quantitative effect of the formulation factors on the dependent variables are represented in Equation (2) and also shown in Table 8. Factor A (Gellan gum) showed a positive effect on floating lag time, which means that as the concentration of Gellan gumincreased, floating lag time also increased. However, factor B (Carbapol 934 P) showed a negative impact on floating lag time, indicating an inverse relationship between factor and response.. The effect of the factors on floating lag time is represented by the fitted linear regression given in Equation (2) by the software. The ANOVA results for predicting floating lag time are shown in Table.

Floating lag time (min) = + 40.42–71.25A[1] + 1.45 A[2] –36.44 B[1] − 1.07 B[2]

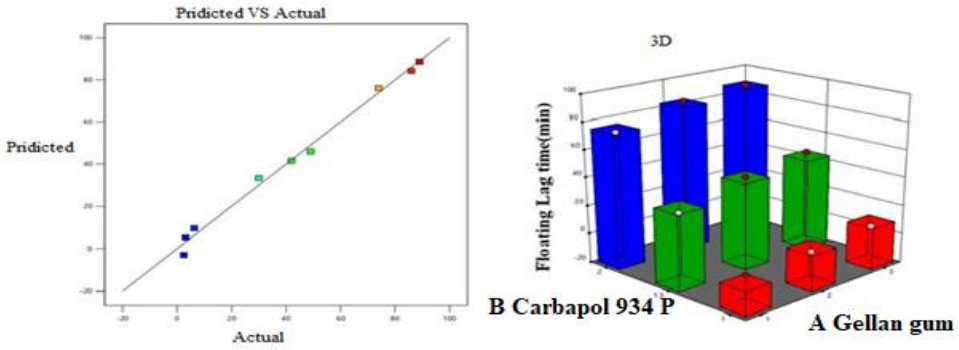

Fig.4 Predicted and actual value plots and 3D response surface plots showing the effect of independent variables, i.e., factor A (Gellan gum) and factor B (Carbapol 934 P), on response floating lag time.

Impact of Independent Variables on Percentage Water Uptake Response

From the results obtained for percentage water uptake study, it was observed that all formulations behaved differently at a different time interval. At 60 min, the percentage water uptake for F1, F2, and F3 was 33, 23.5, and 16%, respectively, showing that % water uptake decreased with increasing sodium alginate concentration. At 120 min, the % water uptake by F1 increased to 44% and F3 increased to 42%, but for F2 there was no increase in % water uptake. When formulations F1, F4, and F7, which had had the same concentrations of Gellan gumand different concentrations of Carbapol 934 P, were compared with each other, it was observed that as the amount of Carbapol 934 P increased from 1 to 2 g, the percentage water uptake decreased from 44% to 10% at 120 min. Also evident from the results is that formulations F3, F6, and F9 showed 42, 15, and 7.2% water uptake, respectively, at 120 min. The ANOVA results for predicting % water uptake are shown in Table 8. The percentage water uptake study results of the oral raft-forming in situ gelling system of the ABZ formulations are shown in Table 9. Both factors, Gellan gumand carbapol 934 P, had negative effects at higher concentrations on percentage water uptake: As the concentration of factors increased, % water uptake decreased, as shown in Tables 6 and 7. However, both factors showed a positive effect at a lower level of concentration, as seen in Equation (3). Predicted and actual value plots and 3D response surface plots showing the effect of independent variables, i.e., factor A (Gellan gum) and factor B (Carbapol 934 P), on percentage water uptake at 2 h are shown in Figure 6. Hence, from the

noted results and coefficient table, it was evident that Carbapol 934 P had negative effect on % water uptake. The effect of factors on % water uptake is represented by the fitted linear regression in Equation (3) given by the software.

% Water uptake at 2 h = + 20.84 + 1.76 A[1] − 2.54 A[2] + 10.09 B[1] − 5.51 B[2] (3)

Table9 Percentage water uptake study results of the oral raft-forming in situ gelling system of ABZ

S.No.	Formulations	%Water Uptake		
		At 30 min	At 60 min	At 120 min
1	F1	5.5 ± 0.41	31 ± 0.49	41 ± 0.76
2	F2	13.6 ± 0.11	21.5 ± 0.28	5.8 ± 0.42
3	F3	14 ± 0.02	14 ± 0.12	45 ± 0.71
4	F4	5.4 ± 0.14	5.5 ± 0.18	10 ± 0.18
5	F5	0 ± 0.96	16.3 ± 0.08	14.3pol± 0.22
6	F6	25 ± 0.28	15.79 ± 0.32	12.7 ± 0.32
7	F7	0.77 ± 0.21	3.2 ± 0.63	11.82 ± 0.43
8	F8	3.26 ± 0.17	10.5 ± 0.42	10 +.87 ± 0.21
9	F9	11 ± 0.28	4.6 ± 0.28	4.2 ± 0.11

* Mean ± SD, n = 3.

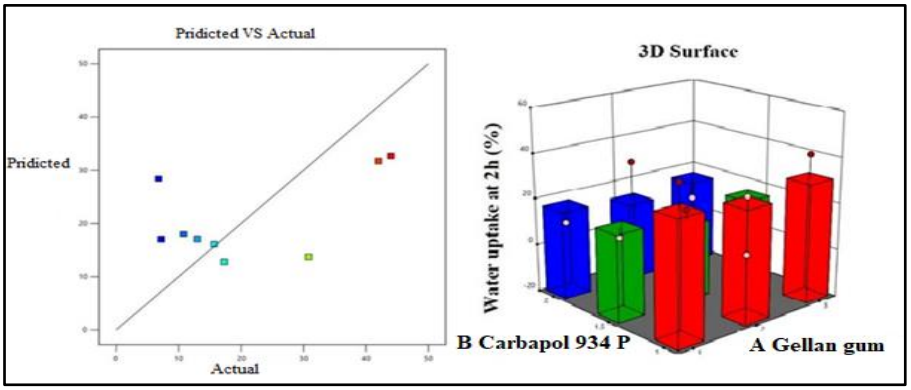

Fig. 5 Predicted and actual value plots and 3D response surface plots showing the effect of independent variables, i.e., factor A (Gellan gum) and factor B (Carbapol 934 P), on % water uptake response at 2 h.

Impact of independent variables on % drug release response at 6 h and at 12 h.

In the developed oral raft-forming in situ gel formulation, the gelling agents employed were Gellan gum and Carbapol 934 P. The gel formation takes place at an acidic pH; when the formulation is administered orally the sol-to-gel transition occurs, and due to the release of CO2 because of the presence of sodium bicarbonate in the formulation, it helps the gel formed by the polymer to float on the surface of the gastric medium, thereby preventing direct contact of the drug with the mucosal layer and leading to sustained release of the drug. The % drug release responses at 6 h and at 12 h were used to identify the effect of factors A and B at three different levels. From the results obtained by the software and Equations (4) and (5), it was observed that both the factors had a positive impact on the % drug release at 6 h and at 12 h. However, factor A at its lowest concentration showed a negative effect on the response. The predicted and actual value plots and 3D response surface plots showing the effect of independent variables, i.e., factor A (Gellan gum) and factor B (carbapol 934 P), on percentage drug release at 6 h and 12 h are shown in Figure 6.

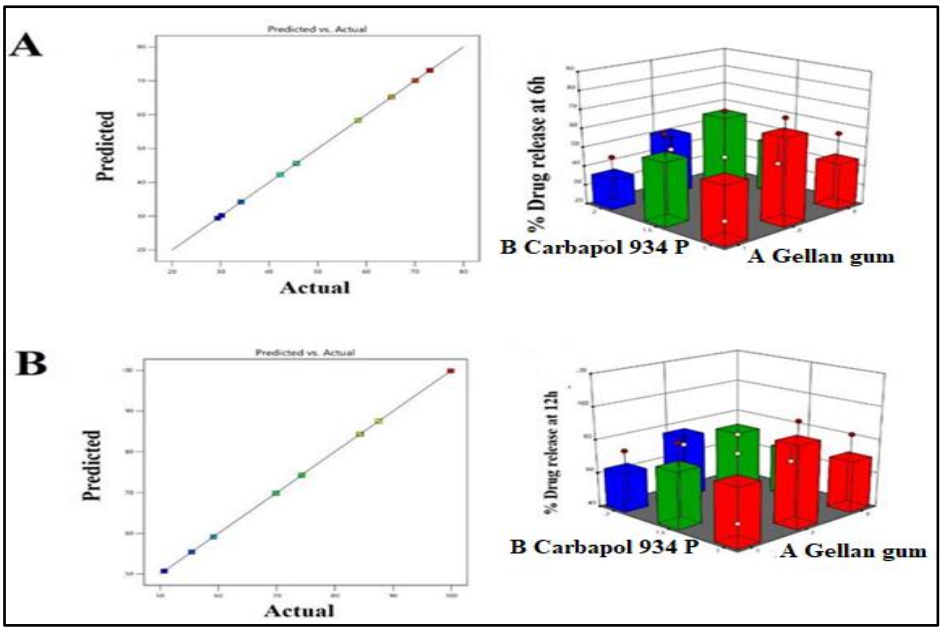

Fig. 6 Predicted and actual value plots and 3D response surface plots showing the effect of the independent variables, i.e., factor A (Gellan gum) and factor B (Carbapol 934 P), on response % drug release at 6 h (A) and % drug release at 12 h (B).

The ANOVA results for predicting % drug release at 6 h and 12 h are shown in Table 8. The fitted linear regression equation showing a significant effect on the % drug release response at 6 h and 12 h are shown below.

- % Drug release at 6 h = + 47.823.09 A[1] + 10.01 A[2] + 1.78 B[1] + 4.68 B[2] (4)
- % Drug release at 12 h = + 71.96 − 1.10 A[1] + 08.75 A[2] +2.35 B[1] + 1.05 B[2] (5)
- Optimization: The effect of various levels of independent variables on the responses can be analyzed by desirability and optimization approaches. Constraints were applied to the dependent variables to achieve an optimized formula by generating desirability plots, as shown in Figure 6.

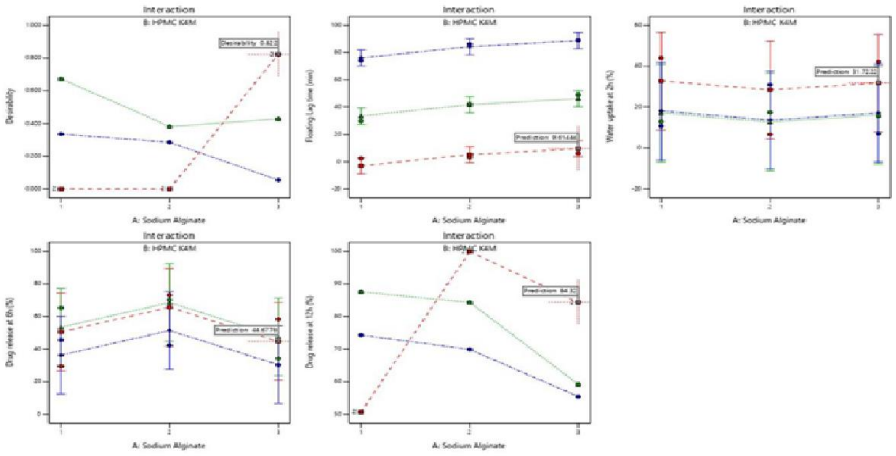

Fig.7.Optimizationoftheoralraft-forminginsitugellingsystemof ABZ,representedby desirability plots and interactions.

Oral Gel (ABZ) plasma concentrations.

The parent drug ABZ, was detected in the plasma of both orall gel and oral solution treated groups. In the 12 h samples, ABZ levels were significantly($p<0.001$) higherafteroraladministration.TheAUC values of both groups were very low and did not show significantdifferences.TheTmaxofABZwassimilarinthe 2 groups, while the Cmax of the oral group was higher than that of the i.p. group but not significantly.

Solution Oral (ABZ-SO) plasma concentration. The concentration of the major metabolite, ABZ-SO in plasma from the oral groupwas greater than that of the other group. Oral administration resulted in significantly higher plasma concentration($p<0.05$)at12hand16h.ThemeanAUC inthe solutionoral .groupwasmuchlowerthanthatoftheoral group; the

AUC of the SO group was 508.33 Ìg/ml/hwhereastheoralgroupwas0810.43Ìg/ml/h.TheCmaxofSOgroupwasat14.84Ìg/mlcomparedwith theoralgroupat39.86Ìg/ml,theoralgroup was more than 2-fold higher than the SO group. In the oral group, there was a trend for C-max being reached soonerthan in the SO group.

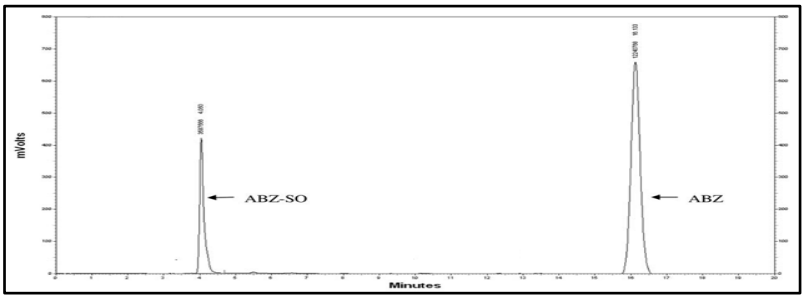

Fig. 8. Standard chromatogram of ABZ and metabolites using HPLC fluorescence detection: ABZ (16.1. min), ABZ-SO (4.05 min)

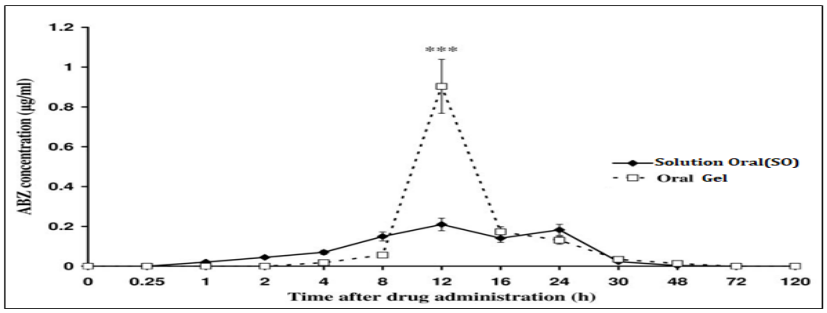

Fig. 9Plasma ABZ concentrations following solution oral or oral administration of the drug. Each point (n=4) represents the mean±SE. At 12 h time point, ABZ plasma concentration was much higher in the orally administered group (*p<0.001 by Student's t-test).**

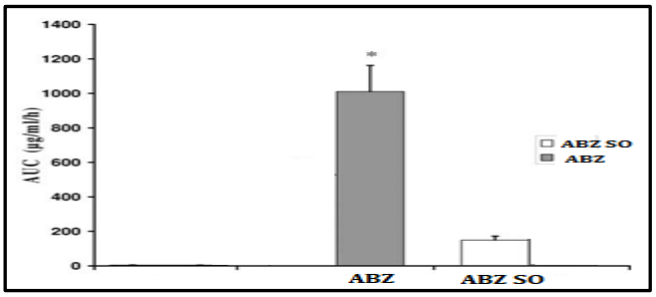

Fig. 10. AUC of ABZ, ABZ-SO orally administered groups (*p<0.05). There were significant differences in AUCs of ABZ or ABZ-SO in these groups.

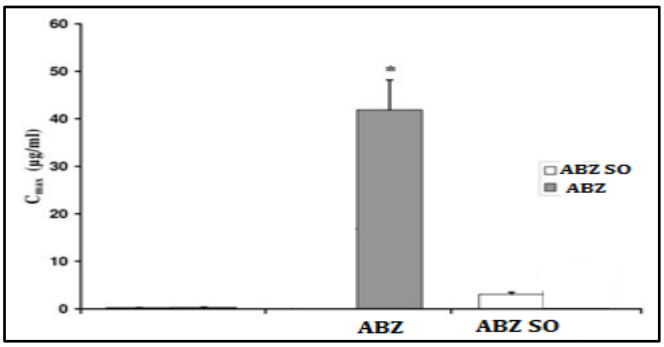

Fig. 11. Cmax of ABZ, ABZ-SO in oral administered groups,Cmax of ABZ was significantly higher in the oral group (*p<0.05).

Table9Stabilitydataofoptimizedformulation ABZunderlongterm stability conditions (30±2°C/65±5%RH)

S.No		Long term stability (30±2°C/65±5%RH)

	Stability testing	0 month	3months	6months
1	Physical	No colour change	No colour change	No colour change
2	% Drug Content	97.94±0.21	97.37±0.18	97.15±0.03
3	Floating time in	10±0.01	10±0.23	10±0.33
4	Viscosity in cps	423±0.10	422±0.15	421±0.20
5	Gel strength in	8.82±0.12	8.78±0.15	8.73±0.17

Note: ± SD (n=3)

Table10Stabilitydataofoptimizedformulation ABZ Accelerated stability conditions (40±2°C/75±5% RH)

		Accelerated stability (40±2°C/75±5% RH)		
S.No	Stability testing on	0 month	3months	6months
1	Physical appearance	No colour change	No colour change	No colour change
2	% Drug Content	97.94±0.21	97.14±0.17	97.03±0.35
3	Floating time in hrs	10±0.01	10±0.37	10±0.51
4	Viscosity in cps	423±0.10	421±0.28	420±0.36
5	Gel strength in N/m2	08.82±0.12	08.75±0.23	08.68±0.28

Note: Mean ± SD (n=3)

Table11%DrugreleaseofABZ formulationinlongtermand accelerated stability conditions for 0, 3 and 6 months of time interval

	% Drug release of ABZ (long term stability)			% Drug release of ABZ (accelerated stability)		
Time	(30±2°C/65±5% RH)			(40±2°C/75±5% RH)		
	0 months	3 months	6 months	0 months	3 months	6 months
1	23.85±0.01	23.74±0.11	23.71±0.21	23.85±0.01	23.70±0.31	23.69±0.12
2	34.19±0.06	34.17±0.06	34.13±0.06	34.19±0.06	34.11±0.04	34.20±0.06
3	41.18±0.15	41.14±0.14	41.11±0.16	41.18±0.15	41.10±0.13	41.19±0.15
4	48.75±0.17	48.65±0.11	48.64±0.18	48.75±0.17	46.62±0.17	48.68±0.17
5	56.26±0.04	56.24±0.24	56.23±0.03	56.26±0.04	56.21±0.02	56.29±0.04
6	65.12±0.07	65.10±0.57	65.09±0.17	65.12±0.07	65.06±0.15	65.05±0.07
7	71.26±0.09	71.22±0.29	71.21±0.28	71.26±0.09	71.20±0.09	71.19±0.09
8	78.12±0.02	78.11±0.32	78.10±0.12	78.12±0.02	78.09±0.02	78.07±0.02
9	83.26±0.03	83.25±0.02	83.22±0.01	83.26±0.03	83.21±0.03	83.20±0.03
10	91.56±0.01	91.53±0.31	91.52±0.11	91.56±0.01	91.51±0.01	91.50±0.01
11	96.62±0.10	95.61±0.16	95.60±0.13	95.62±0.10	95.61±0.10	95.60±0.10
12	97.85±0.09	97.83±0.28	97.82±0.12	97.85±0.09	97.81±0.09	97.80±0.09

All the formulation values ±SD (n =6)

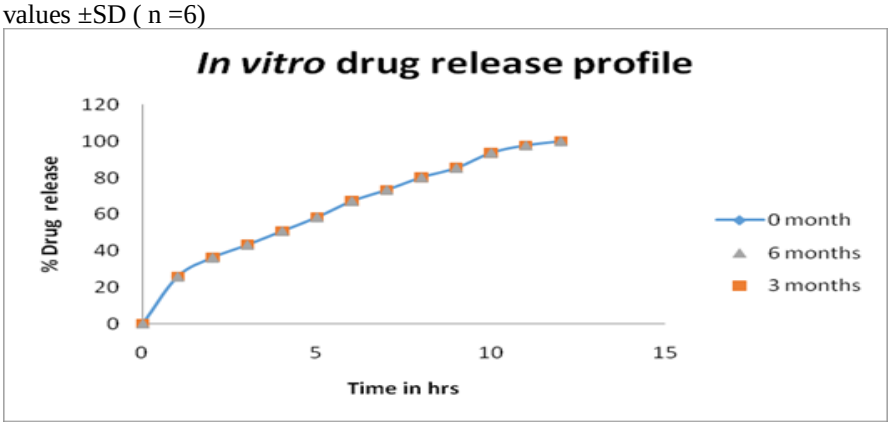

Fig. 12% Drug release of ABZ (long term stability)

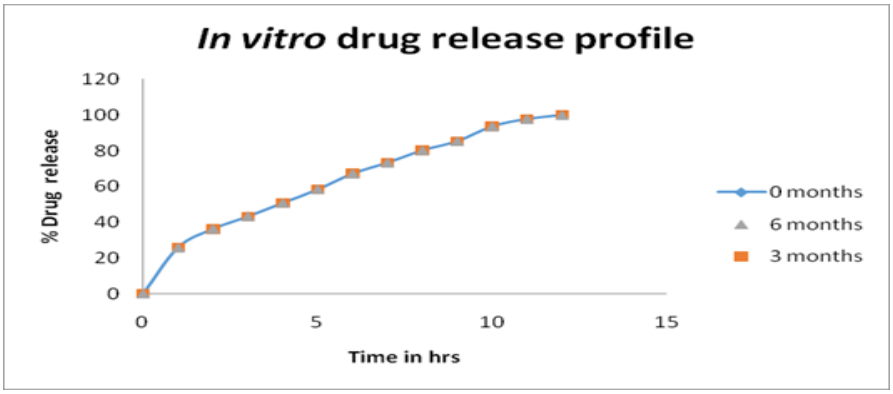

Fig. 13% Drug release of ABZ (accelerated stability)

CONCLUSION

The oral raft-forming in situ gelling system of antuihelmentic drug ABZwas successfully developed using 32 factorial designs. The developed in situ gel formulations exhibited a pH value near 7. The in vitro gelation of an in situ gel formulation showed immediate gelation, and the gel was retained for an extended period of time. From the obtained results of the three-level (32) factorial design analyzing the impact of two independent variables viz. Gellan gum [A] and Carbapol 934 P [B], it was evident that both the selected factors had a significant effect on the chosen responses, such as floating lag time, water uptake (%), and percentage release of drug, supporting the precision of the design employed for optimization. Thus, the developed oral raft-forming in situ gelling system ofABZ may be a favorable and alternative strategy to enhance gastric retention and sustained release of the drug by letting it remain floating in the stomach, thereby augmenting the therapeutic efficacy of ABZ.

The optimized formulation was subjected to different temperature and relative humidity conditions as specified by the ICH guidelines. For long term stability studies, the formulation was stored at 30±2°C with a relative humidity of 65±5%. For accelerated stability studies, the storage conditions were set at 40±2°C with a relative humidity of 75±5%.

Throughout the stability period, the optimized formulation was monitored for any significant changes in physical appearance, drug content, drug release percentage, viscosity, in vitro gel response, and in vitro drug release at different time intervals (0 month, 3 months, and 6 months). The stability data revealed that there were no notable changes observed in any of these parameters, indicating that the optimized formulation remained stable under the specified stability storage conditions as per the ICH Guidelines.

REFERENCES

1. Hani U, Rahamathulla M, Osmani RA, Begum MY, Wahab S, Ghazwani M, Fatease AA, Alamri AH, Gowda DV, Alqahtani A. Development and characterization of oral raft forming in situ gelling system of neratinib anticancer drug using 32 factorial design. Polymers. 2022 Jun 21;14(13):2520.
2. Peppas N, Langer R. New challenges in biomaterials. Science 1994;263:1715-20.
3. Pande SD, Vaidya KP, Gulhane KP. Floating drug delivery system (fdds): a new way for oral drug delivery system. Int J Pharm ClinSci 2013;3:1-13.
4. Nidhi D. In-situ gel: a novel approach of gastro retentive drug delivery. Asian J Pharm Sci Res 2013;3:1-14.
5. Plourde F, Motulsky A, Couffin-Hoarau AC, Hoarau D, Ong H, Lerour JC. The first report on the efficacy of l-alanine based In- situ-forming implants foe the long-term parenteral delivery of drugs. J Controlled Release 2005;108:433-41.
6. Khan AD, Meenakshi B. Floating drug delivery system: an overview. Int J PharmTech Res 2010;2:2497-505.
7. Miyazaki S, Endo K, Kawasaki N, Kubo W, Watanale H, AttwoodD. Oral sustained delivery of paracetamol from in situ gelling xyloglucan formulations. Drug Dev Ind Pharm 2003;29:113-9.
8. Modi SA, Gaikwad PD, Bankar VH, Pawar SP. Sustained release drug delivery system: a review. Int J Pharm Res Dev 2011;2:147-60.
9. MoinAfrasim, Shiva kumar HG. Formulation of sustained release Diltiazem matrix tablet using hydrophilic gum blends. Top J Pharm Res 2010;9:283-91.
10. NayakAmitkumar, MajiRuma, Das Biswarup. Gastroretentive drug delivery system: a review. Asian J Pharm Clin Res 2010;3:1-10.
11. Madan M, Bajaj A, Lewis S, Udapa N, Baig JA. In-situ forming polymeric drug delivery. Indian J Pharm Sci 2009;71:242-51.
12. Thomas LM. Formulation and evaluation of floating oral in-situgel of metronidazole. Int J Pharm PharmSci 2014;6:265-9.
13. Hasan MJ, Kamal BA. Formulation and evaluation of ranitidine hydrochloride are floating In situ gel. Int J Pharm PharmSci 2014;6(Suppl 2):401-5.

14. Shivaraju, Parthiban S, Senthilkumar SK. Preparation and evaluation of ornidazole in situ gelling system for gastro retentive drug delivery. Int J Pharm 2013;3:62-9.
15. Al-Mamun MA, Rahman MR, Biswas S, Kundu SK, Rayhan J. Formulation and bioequivalence evaluation of an extended release solid drug delivery system for metronidazole using usingeudragit nm30d and methocel premium K4m as retardant material. Am J Adv Drug Delivery 2014;2:39-51.
16. Patel DM, Patel CN. Formulation and evaluation of floating oralin-situ gelling system of amoxicillin. ISRN Pharm 2011;1:1-8.
17. Patel JK, Chavda JR, Modasiya Mk. Floating in-situ gel based on alginate as a carrier for stomach specific drug delivery of famotidine. Int J Pharm Sci Nanotech 2010;3:1092-104.
18. Choi BY, Park HJ, Hwang SJ, Park JB. Preparation of alginate boads for floating drug delivery system: effects of CO2 gas- forming agents. Int J Pharm 2002;239:81-91.
19. Google J, Vandrbist F, Amighi K. Development and evaluation of new multiple-unit levodopa sustained–release floating dosage forms. Int J Pharm 2007;334:35-41.
20. Rajinikanth PS, Mishra B. Floating in-situ gelling system for stomach site-specific delivery of clarithromycin to eradicate Helicobacter pyroli. J Controlled Release 2008;125:33-41.
21. Cai ZY, Galettis P, Lu Y, Morris DL, Pourgholami MH. Pharmacokinetics of albendazole in New Zealand white rabbits: oral versus intraperitoneal administration. Anticancer research. 2007 Jan 1;27(1A):417-22.