Floating microspheres of Miglitol as gastro retentive drug delivery system: 32 full factorial design and in vitro evaluation

Cheran K (kcherankumar112@gmail.com)
KLE Society's College of Pharmacy - JNMC Campus: KLE Society's College of Pharmacy
https://orcid.org/0000-0002-4876-120X
Udaykumar B Bolmal
KLE University's College of Pharmacy: KLE Society's College of Pharmacy
Archana S Patil
KLE Society's College of Pharmacy - JNMC Campus: KLE Society's College of Pharmacy
Umashri A Kokatanur
KLE University's College of Pharmacy: KLE Society's College of Pharmacy
Rajashree S Masareddy
KLE University's College of Pharmacy: KLE Society's College of Pharmacy

Research Article

Keywords: Miglitol, Double emulsion method, Ethyl cellulose, Eudragit E100, PVA

Posted Date: October 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-826326/v1

Abstract

Background: The goal of this study was to develop a gastro retentive floating drug delivery system that would improve site specific activity, patient compliance and therapeutic efficacy.

Methodology: Floating microspheres of Miglitol were formulated by double emulsion method using ethyl cellulose and eudragit E100 different weight ratio and PVA as an emulsifier. It has been prepared with respect quantity of polymer concentration and stirring speed to evaluate for % buoyancy, drug entrapment efficiency, particle size drug release rate.

Result: The percent of buoyancy, drug entrapment efficiency, particle size, and percentage yield were increased with increase the polymer mixture concentration. Among all formulation batches, F6 showed acceptable results drug entrapment efficiency (86.57%) and buoyancy (94.25%). F10 formulation was prepared to check the predicted and actual factors and compared with optimized formulation F6. The drug release was increased as the polymer concentration was decrease. The kinetic model zero order had the highest regression coefficient value, it was described as a sustained release dosage form. According to ICH guideline accelerated stability studies of F6 and F10 formulations were conducted for 90 days. After 90 days buoyancy and *in vitro* drug release was performed and the results were F6 and F10 buoyancy was found to be 88.21%, 87.22% and *in vitro* drug release was found to be 62.87%, 63.51%.

Conclusion: The present study, showed compatibility of drug with polymers by FTIR in formulation. Floating microsphere of Miglitol was prepared by double emulsion technique. The **F6** Miglitol floating microsphere was optimized formulation demonstrated with excellent drug entrapment performance (86.57%), good floating behaviour (94.25%), and the largest particle size (670µm). The present study concludes that floating based gastro retentive delivery system of Miglitol microspheres has a safe and effective drug delivery system with increased therapeutic efficacy and a longer duration of action.

Background

The diabetes has become a major health-care issue in India, with an estimated 66.8 million people suffering from it. India ranks third among diabetic population countries. Diabetes mellitus is a chronic disease that is developing at an alarming rate all over the world. Type-2 diabetes, in particular, is causing an increase in the number of patients in every country. Kidney failure, heart attack, stroke and other cardiovascular problems, including coronary artery disease with chest pain, are among the main problems caused by the disease. Various drugs are available for treatment of diabetes mellitus like Metformin, Glipizide, Pioglizone and etc. α- Glycosides inhibitors can decrease the plasma blood glucose level by blocking the oligosaccharide catabolism and lowers the degree of postprandial hyperglycemia example of drugs are Miglitol, Acarbose, and Voglibose[1-4].

Miglitol is a second generation Glycosides inhibitor with the chemical structure 1-deoxynojiromycin. In the microvilli of the intestinal brush border, it serves as a potent competitive inhibitor of alpha-glycosides [5]. Miglitol works by preventing carbohydrates from being digested. It converts disaccharides and

polysaccharides (such as starch, sucrose, and other sugar complexes) into monosaccharides including glucose. Since this effect slows the release of glucose, a high postprandial rise in blood glucose and serum insulin will be reduced. Miglitol has a short biological half- life (2hr) and is absorbed by the intestine. To have the greatest impact, it must be consumed with the main meal. It has a molecular weight of 207.2 and a Pka of 5.9 [6, 8]. Miglitol is classified as a BCS class I compound, which means it is highly soluble and permeable [7]. Miglitol conventional dosage forms available in the market are tablet and film coated tablets. As these dosage forms needs to be administered in multiple doses daily due to shorter half-life of drug, which ultimately reduces patient compliance.

To overcome these disadvantages some of research work has carried out. For instance; Miglitol Sustained release tablet [6], Miglitol Matrix tablet [5], Miglitol oral bioadhesive Controlled release tablet [22]**.** Compared to these developed formulations, the floating microspheres will improve the therapeutic efficacy with drug release in sustained manner. There is a need to establish a formulation that will keep the dosage form in the stomach for a longer period of time and release the drug slowly, resulting in enhanced therapeutic efficacy.

Microspheres are free flowing solid spherical particles with diameters ranging from 1-1000 micrometers. They consisting of proteins or synthetic polymers, which are biodegradable in nature.[11, 25] A well-designed dosage type controlled/sustained drug delivery system should be able to overcome the limitations of traditional therapy while also improving therapeutic efficacy. Each particle is essentially a drug mixture distributed in a polymer using a zero-order release procedure. The dissolution/disintegration of the matrix regulates drug release. Because of the size and shape of the microspheres, they have a ball-bearing effect [12, 24, 27].

Several advantages have been developed to the gastric residence time (GRT) of dosage types, such as the floating drug delivery system (FDDS) or the hydrodynamically balanced system (HBS). Since it has a lower bulk density than gastric fluids, it can float in the gastric juice for an extended period of time without impacting the gastric-emptying rate. In the floating device, the drug is slowly released at a predetermined time, and the residual is excreted after the release is complete [10, 13].

Multiple unit drug delivery systems, such as floating microspheres, are engineered as a sustained drug delivery to increase therapeutic efficacy and oral bioavailability and it has been gaining attention for the uniform distribution of these multiple-unit dosage forms in the stomach, which means better drug absorption and less local stomach discomfort [14, 23]. As per review of literature floating drug delivery system has not been developed yet for this drug.

Thus, in the present study attempts were made to prepare, optimize and evaluate floating microspheres for effective therapeutic efficacy, sustained release of drug with reduced dose frequency and enhanced patient compliance.

Methods

Miglitol was obtained as a gift sample from Hetero Labs Ltd., Baddi, Himachal Pradesh. Ethyl cellulose was purchased from west coast lab, Mumbai. Eudragit E100 was purchased from Evonik pharma industries, Mumbai and Polyvinyl alcohol (PVA), Dichloromethane (DCM), and n-Hexane was purchased from Moly Chem, Mumbai. All other solvents and reagents were used as analytical grade in this analysis.

Factorial Design:

The Design of Experiment (DOE) represented a maximum amount of information in a minimum number of runs. DOE is the easiest and most effective technique for controlling a critical parameter. Various preliminary trail formulations were carried out by varying concentrations of ethyl cellulose and eudragit E100 and also magnetic stirring speeds. On the basis of preliminary studies, the concentration of polymers and magnetic stirrer speed were selected to formulate the microspheres. The selected polymer concentration and stirrer speed were used to engender a 3^2 full factorial (2 factor and 3 levels) screening design, and 9 experiment runs were establish using JMP® software (version 15). There are two independent variables and two dependent variables in this analysis. The concentration of ethyl cellulose (X_1) and concentration of eudragit E100 (X_2) were selected as independent variables (-1, 0, +1). The dependent variables were % buoyancy (Y_1) and drug entrapment efficiency (DEE) (Y_2). Response surface methodology (RSM) was used for the statistical analysis of effects of independent variables on dependent variables using Design-Expert® software (version-13) as shown in Table 1. Using this software screening design, different models were constituted, and the significance of the model was confirmed by statistical parameters. RSM two and three dimensional response counter plot was constituted to read the main effect and interaction between factors and runs [9]. The formulation 10 was prepared as to validate optimized formulation by using actual and predicted value coefficient obtained DOE.

Preparation of Microsphere:

Microspheres were prepared by double emulsion method using water in oil in water emulsion (W/O/W) with different polymer (Ethyl Cellulose & Eudragit E100) ratios [15]. Drug was dissolved in aqueous solvent (Distilled water) and polymer mixture (-1, 0, +1) was dissolved in organic solvent (DCM). Then the aqueous solution was mixed to the organic phase containing the polymer to obtain the primary emulsion (W/O). This primary emulsion was slowly injected (Syringe with 22G needle) into the 100ml of 2% PVA solution under magnetic stirrer (700 rpm, at 30ºC) to prepare the double emulsion (W/O/W). After preparing the double emulsion, 15ml of n-Hexane was added to the microsphere to harden it. The emulsion was held under the magnetic stirrer at the same speed for 5 hours in order to evaporate the organic solvent. The microspheres were then filtered using Whatman filter paper no 44, washed with n-Hexane, and allowed to dry overnight at room temperature [15, 35]. The formulation master formula as given in Table 2.

Characterization floating of Microsphere:

Drug Entrapment Efficiency:

The Miglitol Floating Microsphere of all the formulations were analysed by UV-Visible Spectrophotometer. The 100mg of all floating microspheres were diluted in 20 ml of DCM and with continuous stirring phosphate buffer pH 1.2 was added in divided quantise of 20ml three times to completely dissolve the microspheres. Then the obtain solution was transferred into the separating funnel. In separating funnel the aqueous phase was removed. Whatman filter paper was used to filter the separated aqueous solution. Then the sample was analysed by UV-Visible Spectrophotometer at 220 nm [16]. Then the drug entrapment efficiency was calculated by the given formula [21].

$$\%\ \text{of Drug Entrapment Efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}}\ \text{X100}$$

Percentage of Buoyancy:

The USP type-2 paddle dissolution apparatus was used to achieve the floating behaviour. The 100 mg of all floating microsphere formulations were transferred into the dissolution basket. The 900 ml of phosphate buffer pH 1.2 was used as a floating medium with at 100 rpm up to 12hrs. After 12hrs the floating microspheres on the surface of floating media was filtered and kept for drying at room temperature overnight [16,17, 30]. After drying the microsphere buoyancy was calculated by the given formula.

$$\%\ \text{of Buoyancy} = \frac{\text{Final weight of floating microsphere}}{\text{Initial weight of floating microsphere}}\ \text{X100}$$

Determination of Particle size:

Particle size determination plays an important role in the drug release studies and particle floating property. The floating microsphere shape and particle size were evaluated by optical microscope. With a calibrated ocular micrometre, particle size was measured in the range of 200-700 [20].

Scanning Electron Microscopy:

The dried floating microspheres morphological character of outer and internal surface was analysed by scanning electron microscope (SAIF Karnatak University Dharwad). The particle image was captured at 60X and 100 X magnifications by using electron microscope.

Percentage yield:

The prepared all floating microspheres were collected and weighed. The weighed microsphere was divided by the total weight of initial non- volatile components which we were used for preparation of microspheres (Drug + Polymer) [18]. The provided formula was used to measure the percentage yield.

$$\text{Percentage Yield} = \frac{\text{Weight of floating microspher}}{\text{Total weight of drug and polymer}} \text{X100}$$

Lag time:

The floating microspheres were weighed from various formulations and transferred to a beaker with a pH of 1.2 as the medium. The time taken by floating microsphere to rise to the surface was noted.

***In vitro* drug release study:**

The dried floating microspheres were evaluated by *in vitro* drug release profile. The dissolution was conducted by using the 0.1 N HCl (pH 1.2) and the study was performed up to 12hrs. The dissolution apparatus USP type-2 paddle method was used to assess the drug release study for all formulations. The all different formulations of floating microsphere were weighed and transferred into the dissolution basket. The baskets contain 900ml of pH 1.2 water, which is same as the stomach pH. The rotational speed of the paddle was set to 100 rpm. Every periodic time interval 5ml solution was pipetted out from the dissolution basket and at the same time fresh 5ml dissolution medium was added. Then the sample was diluted with pH 1.2 and analyzed by UV-Visible Spectrophotometer at 220 nm [9].

Release kinetic study:

The kinetic study was performed to determine the mechanism of drug release from floating microspheres. The drug release data were plotted into the different kinetic models, such as zero order, first order, higuchi and korsemeyer-peppas kinetics [29, 31].

Stability Studies:

According to the ICH guidelines stability study was carried out for optimized formulations. Formulations of floating microspheres were held in stability chamber for 90 days with temperature of 40ºC ± 2ºC, and relative humidity of 75% ± 5% [(19)]. After each time interval of 0, 30, 60 and 90 days optimized formulations were evaluated for buoyancy and in-vitro dissolution study [26, 34].

Result

Table 1- Effect of Dependent Variables from Independent Variable

Formulation code	Independent variables		Dependent variables	
	X_1	X_2	Y_1	Y_2
F1	0	0	85.72 ± 0.76	74.21 ± 0.023
F2	+1	0	92.37 ± 0.104	80.45 ± 0.034
F3	0	+1	91.12 ± 0.072	81.32 ± 0.123
F4	-1	+1	84.45 ± 0.143	77.18 ± 0.98
F5	-1	0	77.37 ± 0.041	72.48 ± 0.063
F6	+1	+1	94.25 ± 0.71	86.57 ± 0.078
F7	+1	-1	89.04 ± 0.12	76.64 ± 0.12
F8	0	-1	79.54 ± 0.068	73.73 ± 0.81
F9	-1	-1	73.23 ± 0.092	70.82 ± 0.101

X1 – Ethyl cellulose concentration, X2 – Eudragit E100 concentration

Y1 - % Buoyancy, Y2 – Drug Entrapment Efficiency

[-1, 0, +1] – Low, Medium, High

Table 2- Formulation table based on Design of Experiment 3^2 Full Factorial Design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Miglitol (mg)	75	75	75	75	75	75	75	75	75	75
Ethyl cellulose (mg)	600	700	600	500	500	700	700	600	500	690.85
Eudragit E100 (mg)	600	600	700	700	600	700	500	500	500	674.10
RPM	500	500	500	500	500	500	500	500	500	500
PVA (%)	2	2	2	2	2	2	q2	2	2	2
DCM (ml)	10	10	10	10	10	10	10	10	10	10
Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table 3- Characterization of Miglitol Floating Microspheres

Formulation	DEE (%)	Buoyancy (%)	Particle size (µm)	% yield
F1	74.21 ± 0.023	85.72 ± 0.76	511.04 ± 0.085	94.44±0.076
F2	80.45 ± 0.034	92.37 ± 0.104	644.04 ± 0.12	97.89±0.154
F3	81.32 ± 0.123	91.12 ± 0.072	538.73 ± 0.087	97.15±0.054
F4	77.18 ± 0.98	84.45 ± 0.143	520.87 ± 0.14	96.02±0.12
F5	72.48 ± 0.063	77.37 ± 0.041	453.03 ± 0.13	92.98±0.064
F6	86.57 ± 0.078	94.25 ± 0.71	670.42 ± 0.103	98.76±0.11
F7	76.64 ± 0.12	89.04 ± 0.12	618.34 ± 0.18	97.56±0.062
F8	73.73 ± 0.81	79.54 ± 0.068	432.53 ± 0.112	92.45±0.082
F9	70.82 ± 0.101	73.23 ± 0.092	410.45 ± 0.098	91.65±0.059

Table 4- Drug Release Kinetic Data

Formulation code	Kinetic data (R^2)				
	Zero order	First order	Huguchi	Korsmeyer-	Peppas
				R^2	n- value
F1	0.9898	0.7957	0.8833	0.8667	0.7349
F2	0.9948	0.781	0.9043	0.8521	0.5642
F3	0.9867	0.8095	0.8752	0.8707	0.4540
F4	0.9929	0.7644	0.9041	0.8345	0.6542
F5	0.9948	0.7698	0.9057	0.8459	0.7258
F6	0.9891	0.7826	0.8921	0.8485	0.5726
F7	0.9915	0.7983	0.8909	0.8709	0.8249
F8	0.9919	0.7568	0.9027	0.8249	0.6580
F9	0.9964	0.7598	0.9087	0.83397	0.8553

Table 5- Validation of Optimized formulation F6 with predicted values of DOE, Comparison and Statistical Analysis

Formulation code	Dependent variables	Predicated value	Actual value
Optimized F10	DEE	98.06%	97.45%
	% Buoyancy	93.82%	92.41%

ANOVA

Source	Degree of freedom	Sum squre	Mean squre	F ratio	F
MODEL	3	263.11069	87.7036	38.2324	0.0007
ERROR	5	11.46980	2.2940		
TOTAL	8	274.58049			

Formulation F10 v/s Optimized Formulation F6

Formulation code	DEE (%)	Buoyancy (%)	Particle size (µm)	*In vitro* drug release study (%)
OPTIMIZED F10	85.45 ± 0.092	92.41 ± 0.104	658.37 ± 0.034	69.03 ± 0.102
F6	86.57 ± 0.078	94.25 ± 0.071	670.42 ± 0.103	67.98 ± 0.114

Discussion

FTIR Spectroscopy Analysis:

The FTIR spectra of Miglitol pure drug and optimized formulation (F6) were carried out. The Miglitol pure dug prominent peak at 3392 cm^{-1} and 1235- 1168 cm^{-1} indicates the O-H stretching and bending vibration. C-H stretching vibration prominent peak shown at 2851- 2820 cm^{-1}. C-C stretching vibration peak was showing at 1454 and 1471cm^{-1}. Prominent peak at 1260cm^{-1} and 1140-1020 cm^{-1} indicates C-N stretching and C-O stretching bands were observed [9] Figure 1 (A). The FTIR spectra of optimized formulation floating microsphere were showing imbricate of the Miglitol pure drug characteristic peak in Figure 1 (B). So it was indicating no drug polymer interaction, and Miglitol pure drug was stable in it's nature after encapsulation process.

Characterization floating of Microsphere:

Drug Entrapment Efficiency:

The drug entrapment efficiency of the all formulations of floating microsphere was found to be in the range of 86.57% - 70.82 %. Drug entrapment efficiency was increasing with increase in Ethyl cellulose: Eudragit E100 polymer ratio. Because as the polymer concentration is increased, the polymer coats more drug particles, increasing the drug entrapment efficiency. The DEE percentage is showed in Table 3.

Percentage Buoyancy:

The percentage of buoyancy of the floating microspheres in all formulations was found to be between 94.25% and 73.23%. The % buoyancy was increased due to increase in the polymer mixture concentration. The floating microsphere was floated in the simulated gastric juice for more than 12hrs. This means that the microsphere will be retained on the gastric juice for a longer period of time in order to enhance the gastric residence time of the dosage form. **Table 3** displays the percentage of buoyancy.

Determination of Particle size:

The particle size determination has been carried out for all formulations of floating microspheres, and was found to be in the range from 670.42 µm – 410.45µm. It was observed that as the Ethyl cellulose: Eudragit E100 polymer ratio increased the particle size also increased. Because, the consistency of solution will increase with polymer ratios, resulting in increased particle size. Floating microsphere with mean particle size range from 500µm-1000µm, have been reported to possess higher floating ability [28]. Table 3 showed the measured particle size effects.

Scanning Electron Microscopy:

The optimized floating microsphere (F6) surface morphology was explored by SEM. It has been examined at different magnification of 60X and 100X. The images of microspheres were almost smooth and spherical shape and the small porous cavities were found on the surface of microspheres, which will aid in improving the floating property of microspheres. The F9 formulation of floating microspheres prepared higher ethyl cellulose and eudragit E100 ratios has shown rough surface in SEM images. This is attributed to increased polymer concentration increases particle size with rough surface. It's showed in Figure 2 (A) & (B).

Percentage yield:

The percentage yield of all floating microsphere formulations was calculated. The calculated percentage yield ranged between 98.76% - 91.656%. It indicates that the increased polymer concentration in microspheres leads to increased percentage yield. The calculated percentage yield is showed in Table 3.

Lag time:

All nine formulations were evaluated for floating lag time, and the floating microsphere lag time was zero seconds for all formulations. Because, all the floating microsphere formulations possess floating

property, when they are added to simulated gastric fluid, microsphere will not go into the solvent and it will just float on the simulated gastric fluid. As a result, the floating lag time would be zero second.

In vitro drug release study:

In vitro drug release study of floating microsphere was conducted for 12hrs using 0.1N HCl pH1.2 as a release medium by using USP type-2 dissolution apparatus. After 12 hours, the cumulative drug release of all 9 formulations showed that Formulation F9 had the highest cumulative drug release and Formulation F6 had the lowest cumulative drug release. The increased polymer concentration results in more amount of polymer coating around the drug that ultimately decreases the cumulative percent drug release. The cumulative percentage drug release was performed triplicates and the data was plotted in graph it has shown in Figure 3.

Release kinetic study:

The data was obtained from *in vitro* drug release study and it has plotted in different kinetic models. The all formulations were showing the zero order kinetic model with maximum R^2 value. Zero order kinetic model is the best fit model for sustained release dosage forms. As per the n-value of peppas model which was between 0.5 to 1, so mechanism was non- fickian transport [33]. The kinetic model fitting release profile of all formulation results are given in Table 4.

Stability Studies:

According to ICH guidelines, all formulations were tested for stability for 30, 60 and 90 days. There was slight variation in shown in buoyancy and in-vitro drug of Miglitol floating microspheres on 90^{th} day at (40ºC ± 2ºC and 75% ± 5%). F6 formulations buoyancy was found to be 88.21% and in-vitro drug release was found to be 62.87%. F10 formulations buoyancy was found to be 87.22% and *in vitro* drug release was found to be 63.51%. There were no colour variations in the physical appearance of any of the Miglitol floating microsphere formulations, and there was no overlap on other particles.

Optimization of floating microsphere:

Based on pilot study report, selected polymer concentration and stirring speed Miglitol floating microsphere was prepared by using JMP® software 3^2 factorial designs (3 level 2 factor). Independent variables was polymer concentration A (Ethyl cellulose), B (Eudragit E100) 3 levels (-1, 0, +1) 500, 600, 700 and dependent variables was drug entrapment efficiency and percentage buoyancy. Miglitol floating microsphere was prepared by double emulsion method because of Miglitol is freely soluble in water to confirm with available literature and text books.

The optimization studies were performed in order to select the best polymer concentration of ethyl cellulose and eudragit E100 to obtain the maximum drug entrapment efficiency and buoyancy. As the polymer concentration (ethyl cellulose and eudragit e100) increase buoyancy and drug entrapment also increase simultaneously.

ANOVA was analysed with data, it was obtained that it follows quadratic model R^2 value for % of buoyancy was 0.9866 and drug entrapment was 0.9920.

The Equation for the buoyancy and drug entrapment efficiency 1 and 2 respectively,

$(Y_1) = 85.38 + 6.77\ A + 4.67\ B - 1.50\ AB - 0.3427\ A^2 + 0.1183\ B^2$……. (1)

$(Y_2) = 89.01 + 4.68\ A + 4.48\ B - 1.58\ AB + 0.0567\ A^2 + 2.16\ B^2$…….. (2)

Where, A and B represents the polymer concentration (-1, 0, +1) of Ethyl cellulose and Euduragit E100 respectively.

Statistical analysis of response Y_1 buoyancy shows that the quadratic model F- value is 44.15 it's indicate the model is significant. The value of p should be less than 0.05 obtained p value is 0.0052, this implies the model terms are significant. After examining the quantity of co efficient and the mathematical sign it exhibits, the polynomial equation can be used to reach at a conclusion.

Statistical analysis of response Y_2 drug entrapment efficiency shows that the quadratic model F- value is 74.12 its indicate the model is significant. The value of p should be less than 0.05 obtained p value is 0.0024, this implies the model terms are significant. After examining the quantity of co efficient and the mathematical sign it exhibits, the polynomial equation can be used to reach at a conclusion.

Design space is a multivariate mixture and interaction of independent factors and process factors that has been proved to enable quality assurance. To build design space and optimise all of the replies, a numerical optimization approach (desirability function) and a graphical optimization approach (overlay plot) were utilised.

Constraints on the dependent response and independent factors were used to obtain at the optimum formulation. The response, buoyancy, and drug entrapment efficiency restrictions were fixed at range between 90-95 % and 95-98 %, respectively. As a result, because it falls in the yellow area of the overlay plot, with desirability equal to 1, Formulation F10 was regarded an optimum formulation. The optimised formulation would have a level of X1 (ethyl cellulose) = 690.85 and X2 (eudragit E100) = 674.10, with predicted buoyancy and drug entrapment effectiveness of 93.82 % and 98.06 % respectively. The calculated results value of buoyancy (92.41%) and drug entrapment efficiency (97.45%) were quite similar to the model's expected values. F10 formulation was prepared to check the predicted and actual factors and compared with optimized formulation F6. The data has been optimised, as shown in the Table 5 and Figures 4, 5 and 6 below.

Conclusions

The present study, showed compatibility of drug with polymers by FTIR in formulation. Floating microsphere of Miglitol was prepared by double emulsion technique. The **F6** Miglitol floating microsphere was optimized formulation demonstrated with excellent drug entrapment performance (86.57%), good floating behaviour (94.25%), and the largest particle size (670µm). The F6 formulation showed the drug release profile in sustained manner more than 12hrs. Also F6 formulation has compared with the formulation F10 which was prepared to validate the predicted and actual values and it was found that F6 optimized formulation showed the better results. Formulated Miglitol microsphere were stable at 40ºC ± 2ºC and 75% ± 5% as per stability studies. From the present study, it can be concluded that the prepared floating microspheres remain for a longer period of time in simulated gastric fluid and results in sustained release of drug, resulting in enhanced therapeutic effectiveness and safety with site specific drug delivery. Often, to improve patient compliance, reduce the dose frequency.

Abbreviations

Conc: Concentration; **CDR:** Cumulative drug release; **%:** Percentage; **µg:** Microgram; **mg:** Milligram; **rpm:** Rotation per minute; **DSC:** Differential scanning calorimetry; **FTIR:** Fourier transform infrared; **hr:** Hour; **λmax:** Maximum absorbance; **nm:** Nanometer; **DEE:** Drug Entrapment efficiency; **R^2:** Regression coefficient; **GRT:** Gastrointestinal tract;

Declarations

Ethical approval and consent to participate: Not applicable

Consent for Publication: Not applicable

Availability of data and material: All data and material are available upon request.

Competing interests: The authors declare that they have no any competing interests**.**

Funding: Not applicable- Self funded

Authors' contributions:

All authors (CK, UBB, ASP, UAK, RSM) have contributed for successfully completing the research work. CK and UBB have designed, conducted and monitored the study throughout the completion of study and ASP as corresponding author approved the manuscript from all co-authors. CK has compiled the data and drafted the manuscript. UBB and ASP have assisted in interpretation of the data and substantially revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements:

Authors are thankful to their regards to Dr. Prabhakar Kore Basic Science Research Centre, KLE Academy of Higher Education and Research Belagavi for providing their amenities to carry out this work. The authors are also thankful to Cipla Pvt. Ltd. Bangalore, India, for providing Felodipine pure drug as gift sample. The authors are thankful to Kesar Control System, AICTE-MODROB 2017-2018 for providing stability chamber to carry out the stability studies in research work. Authors are also thankful AICTE-MODROBE for providing Ultrasonic probe sonicator VC750.

References

1. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C (2007). Epidemiology of type -2 diabetes: Indian scenario. Indian J Med Res. 25 (3):217-30.
2. Kaveeshwar SA Cornwall J (2014). The current state of Diabetes Mellitus in india. Australas Medical Journal. 7(1): 45-48. https://dx.doi.org/10.4066%2FAMJ.2013.1979.
3. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das A et al (2001). High prevalence of diabetes and impaired glucose tolerance in india: national Urban Diabetes survey. Diabeotlogia. 44(9): 1094-101. https://doi.org/10.1007/s001250100627.
4. Gupta R, Misra A (2007). Review: Type 2 Diabetes in india: Regional Disparities. The British Journal of Diabetes and Vascular Disease. 7(1): 12-16. https://doi.org/10.1177%2F14746514070070010 30.
5. Yadav N, Panwar MS (2014). Formulation and evaluation of matrix tablets of Miglitol using different grades of HPMC. Asian journal of pharmaceutics. (8):237-40. https://dx.doi.org/10.22377/ajp.v8i4.449.
6. Chauhan M, Jain A, Singh S, Chaurasiya K (2015). Formulation and evaluation of sustained release tablet of Miglitol. World journal of pharmacy and pharmaceutical sciences. vol 4 issue 11, 1194-205. https://dx.doi.org/10.22377/ajp.v8i4.449.
7. Escobar-Jiménez F, Barajas C, De Leiva A, Cano FJ, Masoliver R, Herrera-Pombo J, Hernández-Mijares A, Piñón F, De La Calle H, Tebar J, Soler J (1995). Efficacy and tolerability of Miglitol in the treatment of patients with non-insulin dependent diabetes mellitus. Current therapeutic research. 1; 56 (3):258-68. https://doi.org/10.1016/0011-393X(95)85031-7.
8. Drug Bank https://www.drugbank.ca/drugs/DB00491
9. Waghule RM, Tech M, Naik BJ (2016). Poly-e-caprolactone-loaded Miglitol microspheres for the treatment of type-2 diabetes mellitus using the response surface methodology. Journal of Taibah University Medical Sciences 11(4), 364-73. https://doi.org/10.1016/j.jtumed.2016.03.006.
10. Shakya R, Thapa P, Saha R (2013). *In vitro* and in vivo evaluation of gastroretentive floating drug delivery system of ofloxacin. Asian journal of pharmaceutical sciences.8(3): 191-98. https://doi.org/10.1016/j.ajps.2013.07.025.
11. Dubey M, Kesharwani P, Tiwari A, Chandel R, Raja K, Sivakumar (2012). Formulation and evaluation of floating microsphere containing anti-diabetic drug. International journal of pharmaceutical and chemical sciences. vol 1 (3) 1038-47.

12. Bansal H, Kaur PS, Gupta KA (2011). Microsphere methods of preparation and application, A comparative study. International Journal of Pharmaceutical Sciences Review and Research, Review article – 012. vol 10, 69-78.
13. Ishwarya M, Ramu S, Saravana kumar (2017). Floating microspheres; a promising drug delivery. International journal of pharmacy & pharmaceutical research, Review article. vol 11 (1) , 375-88. https://doi.org/10.12966/ajpps.06.02.2014.
14. Sharma M, Kohil S, Dinda A (2015). In-vitro and In-vivo evaluation of repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer, Saudi pharmaceutical journal. (23), 675-82. https://doi.org/10.1016/j.jsps.2015.02.013.
15. Zubedi SS, Mohammed S (2018). Floating microsphere and its polymer, Journal of drug delivery and therapeutics. 8(5-s): 16-24.
16. Samy AM, Ghorab MM, Shadeed SG, Mohamed NH (2013). Design and optimization ofranitidine hydrochloride floating microspheres, International journal of pharmacy and pharmaceutical sciences. vol 5 (3): 280-84.
17. Giovagnoli S, Blasi P, Schoubben A, Rossi C and Ricci M (2006). Preparation of large porous biodegradable microsphere by using a simple double-emulsion method for capreomycin sulfate pulmonary delivery. International journal of pharmaceutics (Elsevier). 333: 103-11. https://doi.org/10.1016/j.ijpharm.2006.10.005.
18. K Rukhar, A Rikita, O Anup, C Himanusu and U Kumud (2018). Formulation and evaluation of floating microsphere of levofloxacin. International research journal of pharmacy. 9 (7): 186-91.
19. F Nourhn, El Nashar, Doni AA, Mady OY, Maghraby GM (2017). Formulation of clarithromycin floating microspheres for eradication of helicobacter pylori. Journal of drug delivery science and technology (Elsevier). 41: 213-21. https://doi.org/10.1016/j.jddst.2017.07.016.
20. Kumar KP, Garud Naveet (2019). Formulation and evalution of floating microspheres of lovastatin using eudragit-E and ethyl cellulose by solvent evaporation method, Journal of drug delivery and therapeutics. 9(3-s): 46-53. https://doi.org/10.22270/jddt.v9i3-s.2752.
21. Ma N, Xu L, Wang Q, Zhang X, Zhang W, Li Y, Jin L, Li S (2008). Development and evaluation of new sustained release floating microsphere. International journal of Pharmaceutics, Elsevier. 358: 82-90. https://doi.org/10.1016/j.ijpharm.2008.02.024.
22. Deshpande MC, Venkateswarlu V, Babu RK, Triredi RK (2009). Design and evaluation of oral bioadhesive controlled release formulations of Miglitol intended for prolonged inhibition of intestinal α-glucosidase and enhancement of plasma glucogan like peptic-1 levels. International journal of Pharmaceutics (Elsevier). 380: 16-24. https://doi.org/10.1016/j.ijpharm.2009.06.024.
23. Patel B, Kushwaha RS, Jain S (2019). Formulation, Development and Evaluation of Floating Microsphere of Losartan Potassium Using Natural Polymer. Journal of Drug Delivery and Therapeutics. 15;9(3-s):223-8. https://doi.org/10.22270/jddt.v9i3-s.2829.
24. Janjale VR, Patil SR, Fegade TD (2020). A Review on: Floating Microsphere. American Journal of Pharmaceutical Research. 10(02): 232-59.

25. Sharma M, Kohil S, Dinda A (2015). In-vitro and In-vivo evaluation of repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer, Saudi pharmaceutical journal. (23): 675-82. https://doi.org/10.1016/j.jsps.2015.02.013.
26. Tanwar YS, Naruka PS, Ojha GR (2007). Development and evaluation of floating micropsher of Verapamil Hcl. Brazilian Journal of Pharmaceutical Science. 43(4): 529-34. http://dx.doi.org/10.5958/0975-4377.2019.00030.2.
27. Zubedi SS, Mohammed S (2018). Floating microsphere and its polymer, Journal of drug delivery and therapeutics. 8(5-s): 16-24. https://doi.org/10.22270/jddt.v8i5-s.1928.
28. Rokhade AP, Patil SA, Belhekar AA, Halligudi SB, AMinabhavi TM (2007). Preparation and evaluation of cellulose acetate butyrate and poly (ethylene oxide) blend microsphere for gastro retentive floating delivery of Repaglinide. Journal of applied polymer science. 105: 2764-71. https://doi.org/10.1002/app.26456.
29. Kumal VB, Thapa C, Ghimire P, Chaudhari P, Yadhav J (2020). Formulation and optimization of Enalapril Maleate-loaded floating microsphere using Box–Behnken design: in vitro study. Journal of Applied Pharmaceutical Science. 10(08):095-104. : 10.7324/JAPS.2020.10811.
30. Umamaheshwari RB, Jain S, Bhadra D, Jain NK (2003). Floating microsphere bearing acetohydroxamic acid for treatment of H.pyloric. Journal of Pharmaceutical Pharmacological Science. 55: 1607-13. https://doi.org/10.1211/0022357022223.
31. Purohit KK, Garud N (2019). Formulation and evaluation of floating microspheres of lovastatin using Eudragit-E and Ethyl cellulose by solvent evaporation method. Journal of Drug Delivery and Therapeutics. 9(3-s): 46-53. https://doi.org/10.22270/jddt.v9i3-s.2752.
32. Rukhar K, Rikita A, Anup O, Himanusu C and Kumud U (2018). Formulation and evaluation of floating microsphere of Levofloxacin. International research journal of pharmacy. 9 (7): 186-91.
33. Chouhan M, Chundawat AV, Chauhan CS (2017). Development and characterization of floating microspheres of Esomeprazole magnesium trihydrate by solvent evaporation method. International Journal of Pharmaceutical Sciences and Research. 8(2): 686-97.
34. Nourhn F, Nashar EL, Doni AA, Mady OY, Maghraby GM (2017). Formulation of clarithromycin floating microspheres for eradication of helicobacter pylori. Journal of drug delivery science and technology (Elsevier). 41: 213-21. https://doi.org/10.1016/j.jddst.2017.07.016.
35. Kumar KP, Naveet G (2019). Formulation and evalution of floating microspheres of lovastatin using eudragit-E and ethyl cellulose by solvent evaporation method. Journal of drug delivery and therapeutics. 9(3-s): 46-53. https://doi.org/10.22270/jddt.v9i3-s.2752.

Figures

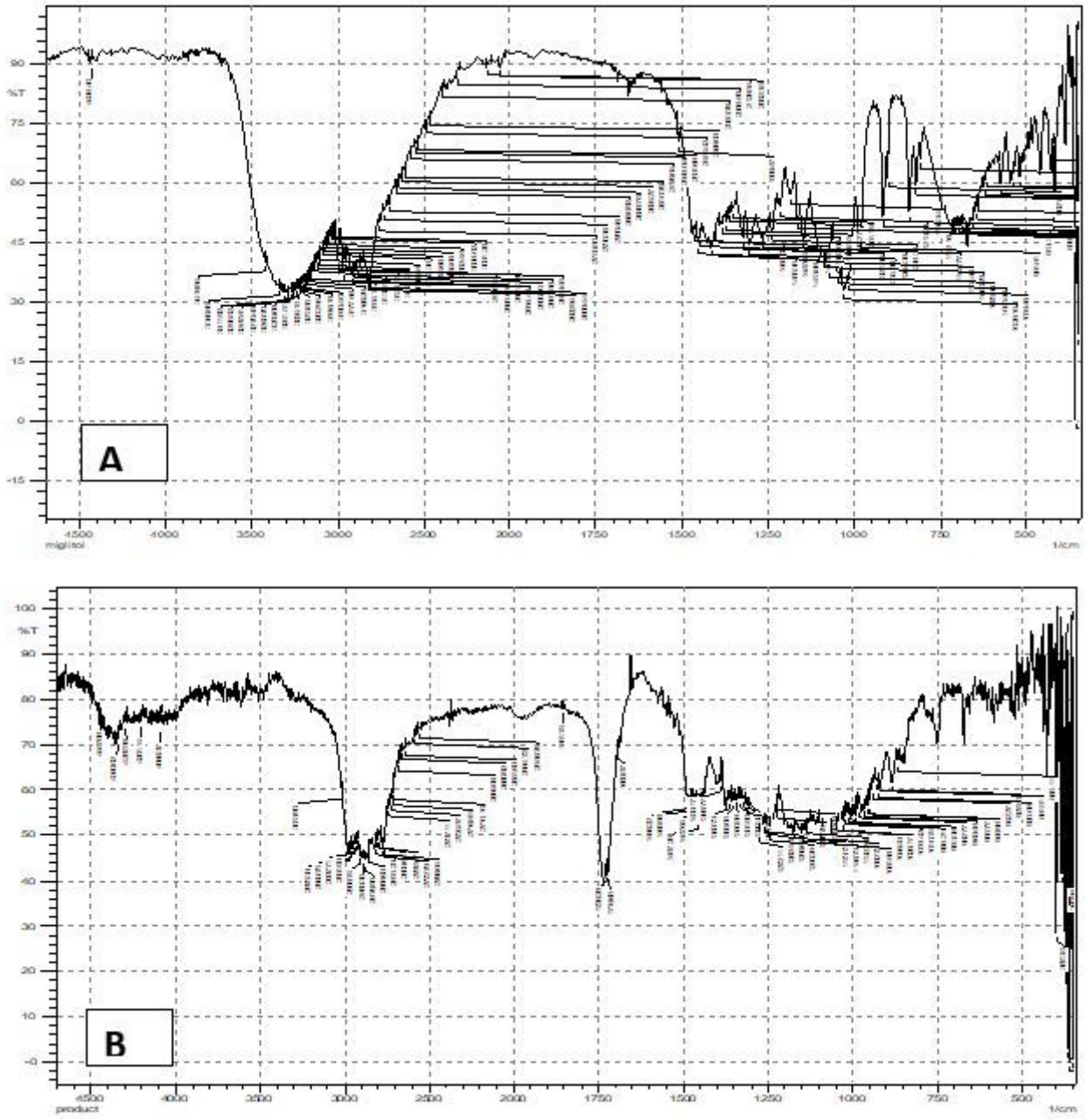

Figure 1

(A) - FTIR spectrum of Miglitol pure drug, (B) - FTIR spectrum of optimized formulation F6

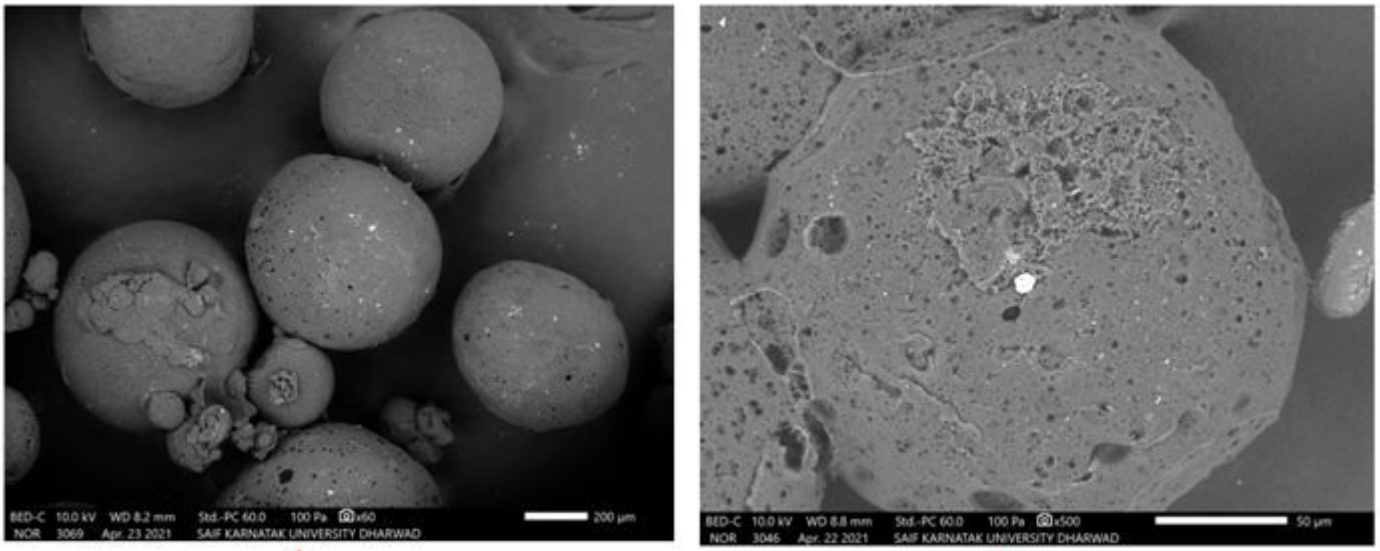

Figure 2

(A) - SEM image of optimized floating microsphere (F6), (B) - SEM image of F9 formulation floating microsphere

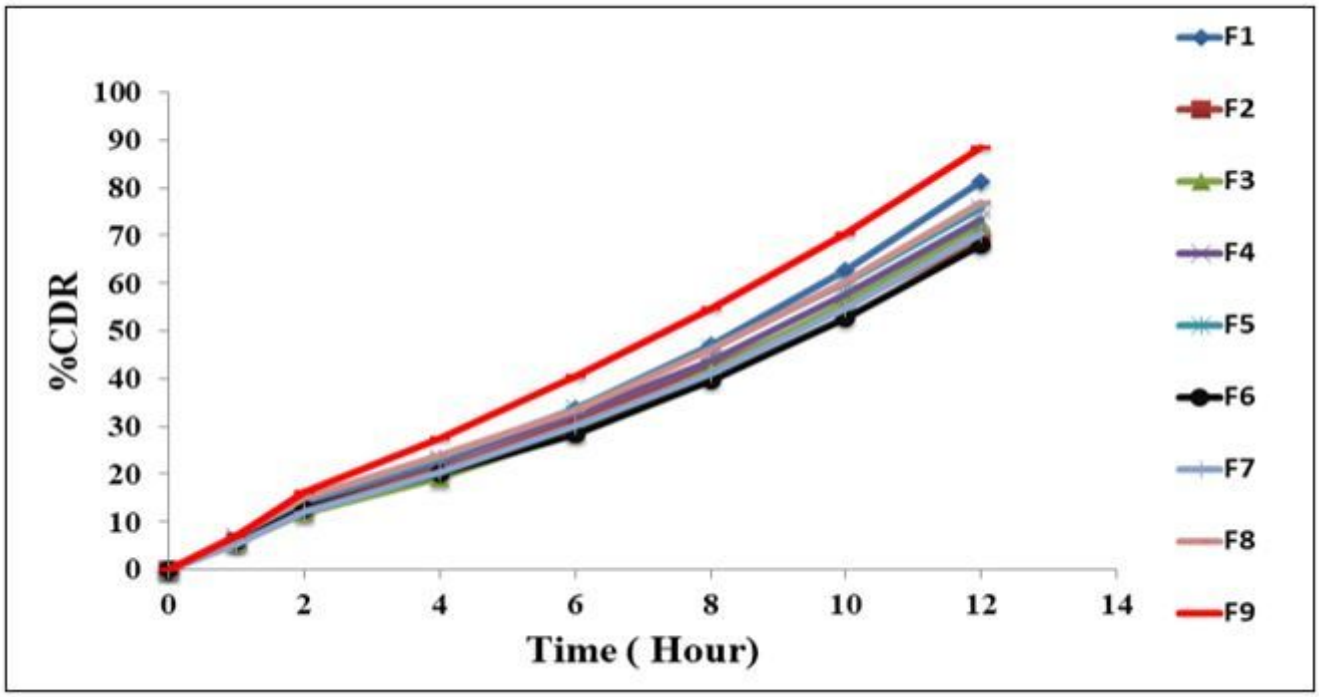

Figure 3

In vitro Drug Release profiles of formulations F1 toF9

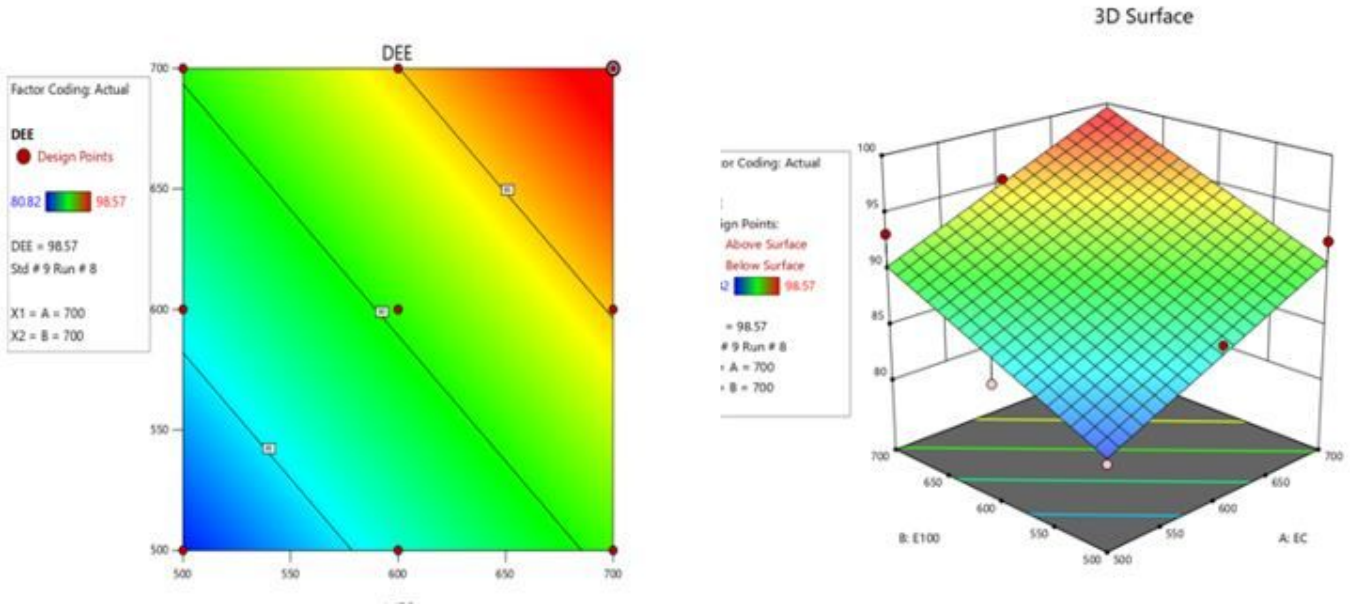

Figure 4

Counter plot for DEE

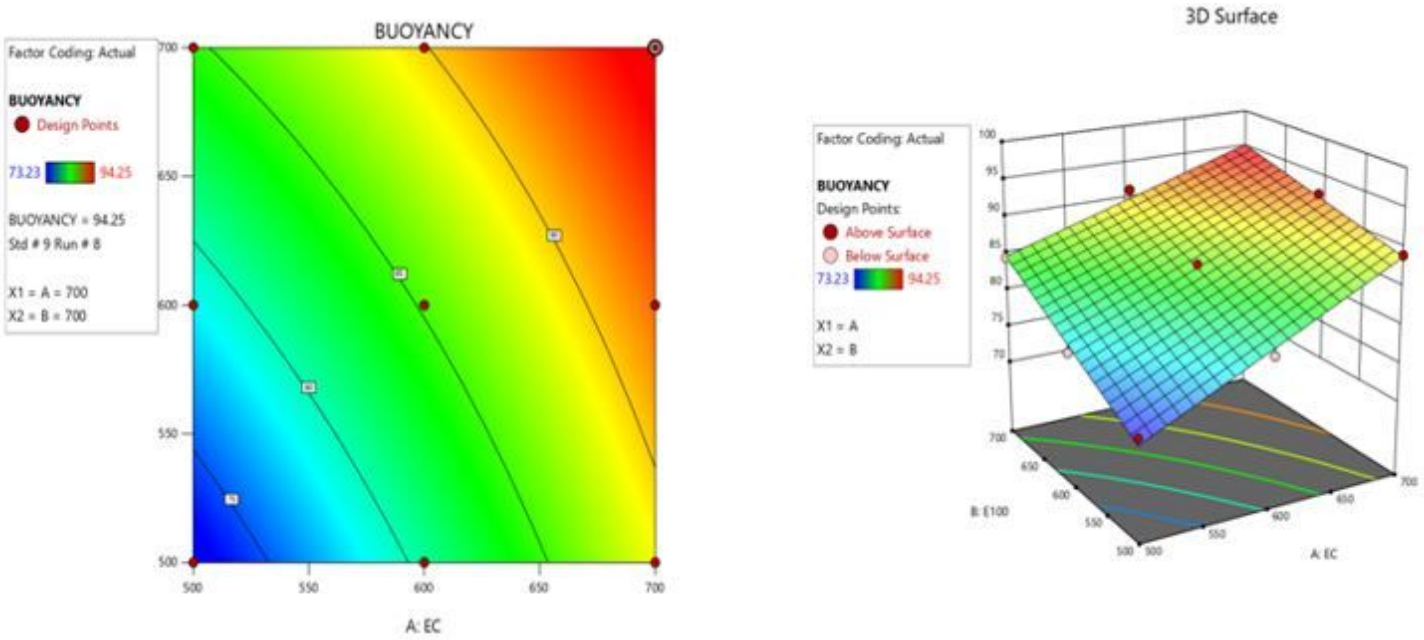

Figure 5

Counter plot for % buoyancy

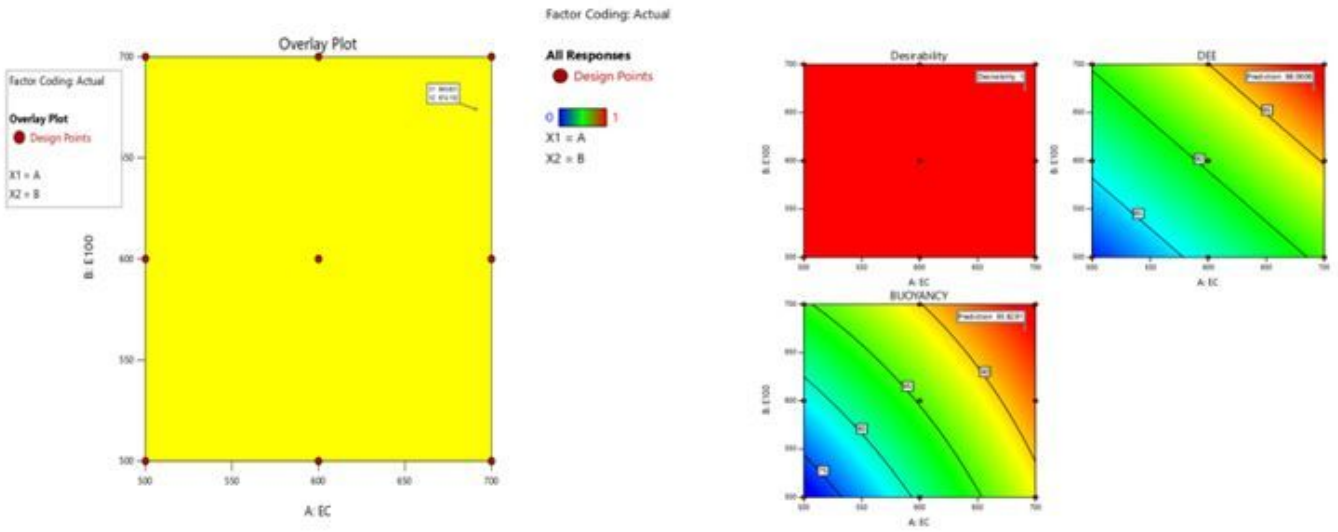

Figure 6

Counter plot for predication factor and overlay plot