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Formulation, Optimization and Evaluation of Gastroretentive Alginate Beads of Ivacaftor by Using Factorial Design

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ABSTRACT

Aim: The main aim of study is to improve solubility of Ivacaftor by formulating into solid dispersions and to prolong the drug release, the solid dispersion of ivacaftor is formulated into gastroretentive alginate beads by Ionotropic Gelation method by using 2^4 factorial design.

Methods: Ivacaftor solid dispersions were prepared by solvent evaporation method using polyethylene glycol, urea and mannitol as carriers by taking 1:1, 1:2 and 1:3 drug:carrier ratios. The best solid dispersion with better dissolution rate was incorporated into gastroretentive alginate beads by Ionotropic Gelation method using 2^4 factorial design. The independent variables are Sodium alginate concentration, Calcium chloride concentration, drug:HPMC ratio and drug:chitosan ratio and the dependent variables are percentage entrapment efficiency and percentage *in-vitro* drug release. The optimization of formulation was carried out using Stat Ease Design Expert Software.

Results: The solid dispersion with polyethylene glycol and drug in 1:2 ratio showed better *in-vitro* dissolution of 98.17% at 120 mins. This solid dispersion was incorporated into gastroretentive alginate beads. The optimized formulation with 2% sodium alginate concentration, 4% calcium chloride concentration, 1:1 ratio of drug:HPMC and 1:1 ratio of drug:chitosan of solid dispersion entrapped alginate beads showed entrapment efficiency of 96.23% and *in-vitro* drug release of 95.62% at 12 hrs. The FTIR studies shown compatibility between drug and the excipients. The drug release kinetics of optimized formulation followed first order with Fickian diffusion.

Conclusion: Ivacaftor entrapped solid dispersion entrapped alginate beads were successfully optimized using 2^4 full factorial design, which gave maximum entrapment efficiency and high drug release for extended period of 12 hrs. The release of ivacaftor was found to follow first order kinetics by Fickian diffusion. It can be concluded that this method may prove to be a suitable potential option for effective delivery of drug for treatment of cystic fibrosis.

Introduction

Solubility is an important criterion which determines the rate of drug absorption, as solubility increases the rate of dissolution increases and enhances the availability of drug at absorption site [1]. Solid dispersions are defined as the dispersions prepared by mixing two or more active ingredients with inert carriers or matrix by fusion or solvent evaporation method. Solid dispersion is an effective method used to enhance the dissolution rate and bioavailability of poorly water-soluble drugs. In solvent evaporation method drug and carrier are dissolved in miscible organic solvent and the solvent is evaporated, the solid particles formed upon cooling are sieved and dried. The carriers used in solid dispersion must be non-toxic, pharmacologically inactive, melt at low temperatures, miscible in wide range of solvents and should have rapid dissolution rate. The solvents used in solid dispersions must be miscible with both drug and carrier, non-toxic and water based systems are preferable [2,3].

In oral controlled drug delivery systems, the drug is released in predetermined rate with predictable and reproducibility in drug release kinetics. In these dosage forms the rate of drug absorption is equal to rate of drug elimination [4]. Gastroretentive drug delivery system increases gastric retention time hence showing site-directed drug release in upper GIT tract for local and systemic action. The rationale of gasteroretentive dosage forms is to prolong gastric residence time to improve the bioavailability of the drugs which are soluble at low pH range [5]. Alginate beads are free-flowing carriers in which drug is dispersed either in solution or in crystalline form that allow sustained release or multiple release profiles. Beads have advantages such as decreasing dosing frequency, improve patient's compliance, reducing side effects, help in local delivery of drug at target site. The techniques used for formulation of sustain release alginate beads are ionotropic gelation method, emulsion gelation method and polyelectrolyte complexation method.

In ionotropic gelation method, it involves the interaction of ionic polymer with the oppositely charge ions by cross linking. The ability of cross linking depends upon the three-dimensional structure and the other groups [6]. Optimization is described as selecting the finest component from set of accessible components. The objective of designing quality formulation is achieved by various optimization techniques like design of experiment. Factorial design is one in which all levels of given factor are combined with all levels of every other factor are combined with all levels of other factor in experiment [7].

Ivacaftor is used for the treatment of cystic fibrosis in patient with second type of mutation (G551D). Ivacaftor binds to and potentiates the channel opening ability of cystic fibrosis transmembrane conductance regulator (CFTR) protein, an ion channel involved in the transport of chloride and sodium ions across cell membrane of lungs pancreas and other organs. Ivacaftor belongs to BCS class-II or BCS class-IV drug, as it has low water solubility (<0.05µg/ml), solubility in ethanol (0.1mg/ml) and solubility in DMSO (25mg/ml) thus solid dispersion technique was selected to enhance the solubility of the drug. Ivacaftor has good oral bioavailability and well absorbed in GITso gastroretentive formulation was selected and its absorption is enhanced by 2 folds on consumption of fat meals. Ivacaftor is also given in combination with lumacaftor and tezacaftor for treatment of cystic fibrosis [8,9]. Hence in this study, we enhanced solubility by formulating into solid dispersion by solvent evaporation method and incorporated into alginate beads by ionotropic gelation method by using factorial design.

Materials and Methods

Materials

Ivacaftor was received as a gift sample from Vertex pharmaceuticals, Hyderabad. Acetonitrile (Fischer Scientific, Mumbai), Polyethylene glycol (SDFCL, Bengaluru), Urea (Fischer Scientific, Mumbai), Mannitol (Fischer Scientific, Mumbai), Sodium alginate (NICE Laboratory, Bengaluru), Calcium chloride (NICE Laboratory, Bengaluru), Chitosan (Research Lab Fine Chem Industries, Mumbai), HPMC K 100M (Yarrow Chem Products, Mumbai), Glutaraldehyde 25% (SDFCL, Bengaluru), Hydrochloric acid (Fisher Scientific, Mumbai) and Deionised water (GP Chemicals, Secunderabad) were the materials used in this study.

Methods

Determination of λ max of Ivacaftor

The 10 µg/ml concentration solution was scanned between the wavelength range of 200-400 nm by using UV spectrophotometer. Ivacaftor λ max was found to be at 255nm.

Construction of calibration curve of Ivacaftor

For construction of calibration curve 5, 10, 15, 20 and 25 µg/ml concentration were prepared by using 0.1 N HCl. These concentrations were checked for absorbance at 255 nm by using UV spectrophotometer. The observed absorbance values were found to be 0.117 (±0.016), 0.255 (±0.046), 0.387 (±0.072), 0.526 (±0.091) and 0.657 (±0.104). The slope and regression values were found to be 0.0265 and 0.9995 respectively [10].

Method for preparation of Ivacaftor solid dispersions

Ivacaftor solid dispersions were prepared to enhance the solubility of ivacaftor. Solid dispersions were prepared by solvent evaporation method. The carrier and drug were dissolved in acetonitrile and the contents were heated at 50° C till the solvent evaporates. The solid film was formed upon cooling, later the powder was collected and sieved through 44 mesh sieve and stored for further use. The formulation table of ivacaftor solid dispersion was shown in table-1. The best formulation was selected based upon *in-vitro* dissolution studies [11-13].

Table-1: Formulation Table of Ivacaftor Solid Dispersion

Solid Dispersion Composition	Method	Drug-Polymer Ratio	Formulation code
Ivacaftor: PEG	Solvent Evaporation Method	1:1	SDP_1
		1:2	SDP_2
		1:3	SDP_3
Ivacaftor: Mannitol	Solvent Evaporation Method	1:1	SDM_1
		1:2	SDM_2
		1:3	SDM_3
Ivacaftor: Urea	Solvent Evaporation Method	1:1	SDU_1
		1:2	SDU_2
		1:3	SDU_3

Formulation of Ivacaftor solid dispersion entrapped alginate beads

For formulation of ivacaftor solid dispersion entrapped alginate beads 2^4 factorial design was selected. The independent variables are sodium alginate concentration with low range of 1% and high range of 3%, calcium chloride concentration with low range of 2% and high range of 4%, drug: HPMC K 100 M and drug: chitosan ratios with low and high ranges of 1:1 and 1:3 ratio. The polymers HPMC K 100M and Chitosan were selected as they form porous membrane which helps to prolong the gastric retention time and also to release the drug in sustained manner. The dependent variables are percentage entrapment efficiency and *in-vitro* drug release.

By keeping all these variables in design expert software, it has shown 16 runs of formulations. The formulation table of ivacaftor solid dispersion entrapped alginate beads was shown in table-2. All the formulations were prepared and evaluated [14,15].

Table-2: Formulation Table of Ivacaftor Solid Dispersion Entrapped Alginate Beads

Formulation Code	Std	Run	Sodium alginate conc (%)	Calcium chloride conc (%)	DRUG: HPMC	DRUG: Chitosan
IB_1	9	1	1	2	1:1	1:3
IB_2	3	2	1	4	1:1	1:1
IB_3	14	3	2	2	1:3	1:3
IB_4	16	4	2	4	1:3	1:3
IB_5	5	5	1	2	1:3	1:1
IB_6	1	6	1	2	1:1	1:1
IB_7	6	7	2	2	1:3	1:1
IB_8	12	8	2	4	1:1	1:3
IB_9	4	9	2	4	1:1	1:1
IB_{10}	8	10	2	4	1:3	1:1
IB_{11}	7	11	1	4	1:3	1:1
IB_{12}	15	12	1	4	1:3	1:3
IB_{13}	11	13	1	4	1:1	1:3
IB_{14}	13	14	1	2	1:3	1:3
IB_{15}	10	15	2	2	1:1	1:3
IB_{16}	2	16	2	2	1:1	1:1

Method for preparation of Ivacaftor solid dispersion entrapped alginate beads

The best ivacaftor solid dispersion (Drug: PEG in 1:2 ratio) was entrapped into alginate beads by ionotropic gelation method. Sodium alginate (gelling agent) solution of required concentration was prepared by dissolving sodium alginate in required quantity of deionised water. To the sodium alginate solution solid dispersion of ivacaftor and polymers HPMC and Chitosan were added and stirred continuously. Later, the solution was sonicated for 5 mins to get homogenous dispersion. The calcium chloride solution of required concentration was prepared and to this solution, sodium alginate solution containing drug was added drop wise by using 18 gauze needle, 1ml of 25% glutaraldehyde (rigidizing agent) was added to calcium chloride (cross linking agent) solution and the entire solution was kept at 400 rpm. After complete addition of alginate solution, the entire solution was kept for stirring for 15 mins. Later, the formed beads were filtered and dried at room temperature [16-18].

Evaluation of Ivacaftor solid dispersions

Formulated solid dispersions were evaluated for percentage yield, drug content and *in-vitro* drug release.

Percentage Yield: Percentage yield can be determined by calculating the initial weight of raw material and the final weight of solid dispersion. Percentage yield can be calculated by using the formula

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{theoritical yield}} \times 100$$

Drug Content: Weighed equivalent to 10mg of ivacaftor solid dispersion and transferred into a beaker added 10ml of 0.1N HCl and stirred for 15 mins with the glass rod. Later the solution was checked for absorbance at 255nm using UV spectrophotometer. From absorbance drug content was calculated.

$$\%\ \text{Drug Content} = \frac{\text{Practical drug content}}{\text{Theoritical drug content}} \times 100$$

***In-vitro* release studies:** The *In-vitro* release studies were carried out by taking weight equivalent to 50mg and placed in muslin cloth tied to paddle and studies were carried out by using USP type II apparatus, maintained temperature at 37 (±2)°C. Sink condition was maintained by withdrawing samples at time interval 15, 30, 45, 60, 90 & 120 mins. The samples were filtered and checked for absorbance at 255nm [19].

Evaluation of Ivacaftor solid dispersion entrapped alginate beads

Formulated Ivacaftor solid dispersion entrapped alginate beads were evaluated for percentage yield, drug content, entrapment efficiency, particle size, FTIR, *in-vitro* drug release and *in-vitro* drug release kinetics

Percentage Yield: Percentage yield can be determined by calculating the initial weight of raw material and the final weight of solid dispersion entrapped alginate beads. Percentage yield can be calculated by using the formula

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$$

Drug Content and Percentage Entrapment Efficiency: Weighed equivalent to 10mg of ivacaftor solid dispersion entrapped alginate beads, transferred into a beaker added 10ml of 0.1N HCl and stirred for 15 mins with the glass rod and the solution was kept overnight. The next day solution was again stirred for 15 mins and was checked for absorbance at 255nm using UV spectrophotometer. From absorbance drug content and entrapment efficiency was calculated.

$$\%\ \text{Drug Content} = \frac{\text{Practical drug content}}{\text{Theoritical drug content}} \times 100$$

$$\%\ \text{Entrapment Efficiency} = \frac{\text{wt. of initial drug} - \text{wt. of final drug}}{\text{wt of initial drug}} \times 100$$

FTIR spectroscopic studies: The compatibility study was carried out for the formulation using FTIR at wavelength range of 4000-400 cm^{-1}. Spectrum for optimized formulation were taken and compared.

Particle size distribution: Average particle size of microbeads was determined by optical microscope along with ocular and stage micrometre. The microbeads were suspended in liquid paraffin and then dispersed on the glass slide and covered with a

coverslip. The average sizes of 50 beads were determined for each formulation using the calibration factor. The average diameter of the beads was calculated using the following formula: $X=\Sigma(X_i)/N$, where X_i=individual diameter of beads; N= number of beads; X= average particle size.

***In-vitro* release studies:** The *In-vitro* release studies were carried out by taking weight equivalent to 50mg and placed in muslin cloth tied to paddle and studies was carried out by using USP type II apparatus. The temperature was maintained at 37 (±2) °C. Sink condition was maintained by withdrawing samples at time interval 0.5, 1, 2, 3, 4, 5, 6, 8, 10 & 12 hrs. The samples were filtered and checked for absorbance at 255nm [20-22].

***In-vitro* drug release kinetics:** The drug release kinetics and mechanism of drug release of Ivacaftor solid dispersion entrapped alginate beads were determined by fitting *in-vitro* release data into various models such as zero order, first order, and Higuchi equations, Korsmeyer- Peppas model [23].

Prediction of optimized formulation

Using the design expert software, the obtained data for each response were analyzed and after optimization of multiple responses, the optimized ivacaftor solid dispersion entrapped alginate beads formulation was predicted, prepared and evaluated for all responses.

Statistical Analysis

Statistical analysis of ANOVA results for 2^4 factorial design were carried out using Stat ease Design Expert Software (version-11). The best fit model was selected based on comparison of several statistical parameters, including the coefficient of variance (CV), coefficient of determination and adjusted R^2. In addition, analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients.

Results and Discussion

Ivacaftor solid dispersions

1. Percentage Yield & Drug Content: The yield of all the formulations was within the range of 73.86% to 96.52% and the drug content of all the formulations were within the range of 52.45% to 85.8%. The values of percentage yield and drug content are shown in Table-3.

2. *In-vitro* Studies: The drug release of all the formulations were in the range of 75.36% to 98.17% up to 120 mins. The dissolution study concluded that the solid dispersions of ivacaftor shown better drug dissolution than the pure drug. The reason behind less amount of dissolution of pure drug is due to its low solubility. The *in-vitro* release studies of ivacaftor solid dispersions were shown in Table-4. Among all the formulations SDP_2 was found to be best and incorporated into alginate beads by using factorial design.

Table-3: Evaluation Results of Ivacaftor Solid dispersions

Formulation Code	Drug: Carrier ratio	Percentage Yield (%)	Drug Content (%)
SDP_1	1:1	87.66	62.6 (±0.24)
SDP_2	1:2	96.52	85.8 (±0.18)
SDP_3	1:3	93.25	72.2 (±0.06)
SDM_1	1:1	73.86	52.45 (±0.08)
SDM_2	1:2	84.02	57.36 (±0.25)
SDM_3	1:3	86.49	69.83 (±0.14)
SDU_1	1:1	78.96	58.69 (±0.02)
SDU_2	1:2	82.87	64.22 (±0.05)
SDU_3	1:3	89.64	79.68 (±0.03)

Table-4: *In-vitro* release studies of prepared solid dispersions of Ivacaftor

Time (mins)	SDP_1	SDP_2	SDP_3	SDM_1	SDM_2	SDM_3	SDU_1	SDU_2	SDU_3
15	28.16 (±0.42)	26.02 (±0.25)	22.48 (±0.15)	28.42 (±0.28)	26.05 (±0.32)	22.01 (±0.24)	28.89 (±0.22)	26.01 (±0.34)	22.01 (±0.36)
30	31.42 (±0.21)	39.13 (±0.18)	53.28 (±0.28)	32.96 (±0.34)	39.58 (±0.15)	36.28 (±0.18)	45.02 (±0.56)	48.31 (±0.26)	59.37 (±0.49)
45	45.21 (±0.46)	52.18 (±0.22)	65.11 (±0.34)	46.12 (±0.42)	48.11 (±0.24)	40.0 (±0.34)	49.3 (±0.25)	53.21 (±0.15)	68.28 (±0.26)
60	59.32 (±0.23)	62.15 (±0.46)	77.32 (±0.23)	51.47 (±0.24)	56.54 (±0.42)	65.21 (±0.51)	52.2 (±0.38)	58.52 (±0.39)	77.65 (±0.21)
90	75.58 (±0.34)	78.16 (±0.15)	85.32 (±0.48)	69.85 (±0.12)	73.26 (±0.19)	79.58 (±0.26)	66.5 (±0.42)	69.43 (±0.23)	84.34 (±0.12)
120	87.69 (±0.56)	98.17 (±0.32)	96.02 (±0.26)	85.15 (±0.22)	89.32 (±0.26)	92.64 (±0.45)	75.36 (±0.12)	79.65 (±0.13)	86.47 (±0.08)

All the values are calculated as Mean, ± S.D, n=3

Ivacaftor solid dispersion entrapped alginate beads

1. Physicochemical characteristics of solid dispersion entrapped alginate beads

The formulated solid dispersion entrapped alginate beads were evaluated for parameters like percentage yield, drug content, entrapment efficiency and particle size. Here all the formulations were prepared with different concentration of sodium alginate, concentration of calcium chloride, drug:HPMC and drug:chitosan ratios. These changes show different percentage yield, drug content, entrapment efficiency and particle size. The percentage yield and drug content of solid dispersion entrapped alginate beads ranged from 66.48% to 93.61% and 42.36% to 68.19% respectively. From entrapment efficiency results it has been observed that the drug entrapment increased with increase in the concentrations of Sodium alginate and Calcium chloride and by decreasing drug:HPMC and drug:chitosan ratio. The entrapment efficiency of solid dispersion entrapped alginate beads ranged from 59.8% to 98.7%. The particle size of solid dispersion

entrapped alginate beads ranged from 1057 µm to 1353.8 µm as tabulated in table-5.

Table-5: Evaluation Results of Solid Dispersion Entrapped Alginate Beads

Formulation Code	Percentage Yield (%)	Drug Content (%)	Entrapment Efficiency (%)	Particle Size (µm)
IB_1	74.26	48.51 (±0.22)	66.1 (±0.14)	1075
IB_2	77.36	52.02 (±0.14)	73.5 (±0.16)	1123
IB_3	86.23	55.60 (±0.18)	87.6 (±0.22)	1228.6
IB_4	91.01	62.15 (±0.06)	96.4 (±0.18)	1153
IB_5	72.14	46.89 (±0.12)	68.86 (±0.16)	1065
IB_6	69.04	45.21 (±0.68)	68.2 (±0.03)	1062
IB_7	87.34	56.28 (±0.14)	91.3 (±0.16)	1276
IB_8	93.61	68.59 (±0.12)	98.7 (±0.12)	1172.5
IB_9	88.54	58.58 (±0.22)	92.3 (±0.14)	1143.4
IB_{10}	92.31	66.24 (±0.12)	98.5 (±0.12)	1158
IB_{11}	79.82	53.22 (±0.16)	82.1 (±0.24)	1151
IB_{12}	78.53	50.74 (±0.25)	70.2 (±0.22)	1106
IB_{13}	82.96	54.28 (±0.32)	84.9 (±0.18)	1223.2
IB_{14}	66.48	42.36 (±0.14)	59.8 (±0.16)	1057
IB_{15}	87.56	58.15 (±0.08)	91.8 (±0.18)	1353.8
IB_{16}	84.63	55.32 (±0.12)	85.2 (±0.14)	1207

2.*In-vitro* Studies: The *in-vitro* drug release of all the formulations exhibited sustained drug release pattern up to 12 hrs, the percentage drug release of all the formulations were within the range of 60.07 (±0.22)% to 98.52 (±0.09)%. The percentage drug release from solid dispersion entrapped alginate beads was affected by various parameters. The percentage drug release in solid dispersion entrapped beads increased with increase in concentration of sodium alginate, calcium chloride and drug:chitosan ratio and by decreasing drug:HPMC ratio. The graphical representation of *in-vitro* release studies of Ivacaftor solid dispersion entrapped alginate beads of all the formulations were shown in figure-1 & 2.

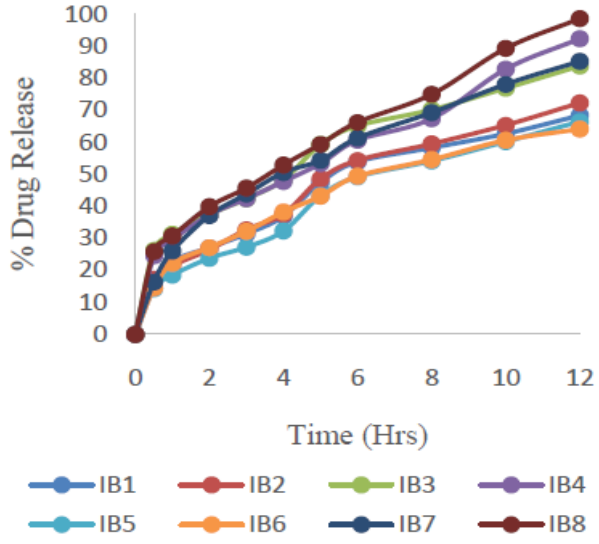

Figure-1: *In-vitro* studies of solid dispersion entrapped alginate beads of the formulations (IB_1 to IB_8)

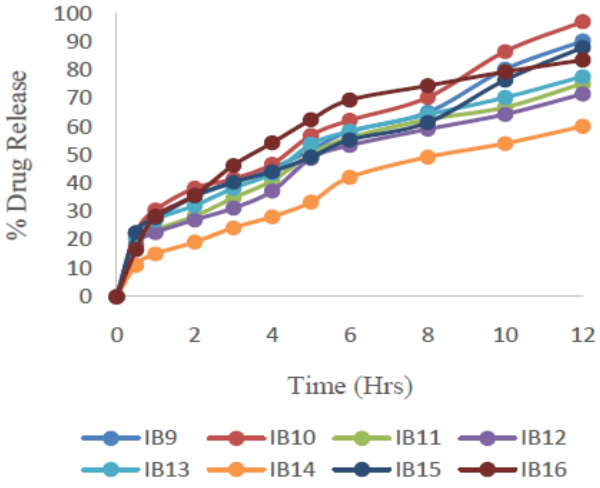

Figure-2: *In-vitro* studies of solid dispersion entrapped alginate beads of the formulations (IB_9 to IB_{16})

Optimized solid dispersion entrapped alginate beads

By entering all the results of entrapment efficiency (response-1) and *in-vitro* drug release studies (response-2) of solid dispersion entrapped alginate beads into design expert software for ANOVA analysis, it has shown the values of probability for selected model as 0.0011 and 0.001 i.e., less than 0.5 for both the responses. R^2 values for response-1 and response-2 were shown to be 0.9142 and 0.9506. Adeq. precision measures signal to noise ratio, a ratio greater than 4 is preferable. The Adeq. precision of both the responses were shown to be 9.8006 and 12.4685.

Precision for both the responses, the selected model was shown significant. The ANOVA analysis of factors along with its effects AB, AC and AD for both the responses were listed in table-6. The effects of these factors on the responses were displayed in contour and 3D response surface plots (Fig no 3 & 4).

Table-6: ANOVA Table for Responses 1 & 2

Source	% Encapsulation Efficiency		% *In- vitro* Drug Release	
	F-value	p-value	F-value	p-value
Model	12.17	0.0011	21.97	0.0001
A- Sodium alginate concentration	68.16	< 0.0001	125.63	< 0.0001
B-Calcium chloride concentration	14.57	0.0051	26.93	0.0008
C-Drug: HPMC	0.0851	0.7780	0.5818	0.4675
D-Drug: Chitosan	0.0480	0.8321	0.1883	0.6758
AB	0.7587	0.4091	0.0003	0.9856
AC	0.7417	0.4142	0.2259	0.6473
AD	0.8575	0.3815	0.2233	0.6492
R^2	0.9142		0.9506	
Adeq. Precision	0.98006		12.4685	

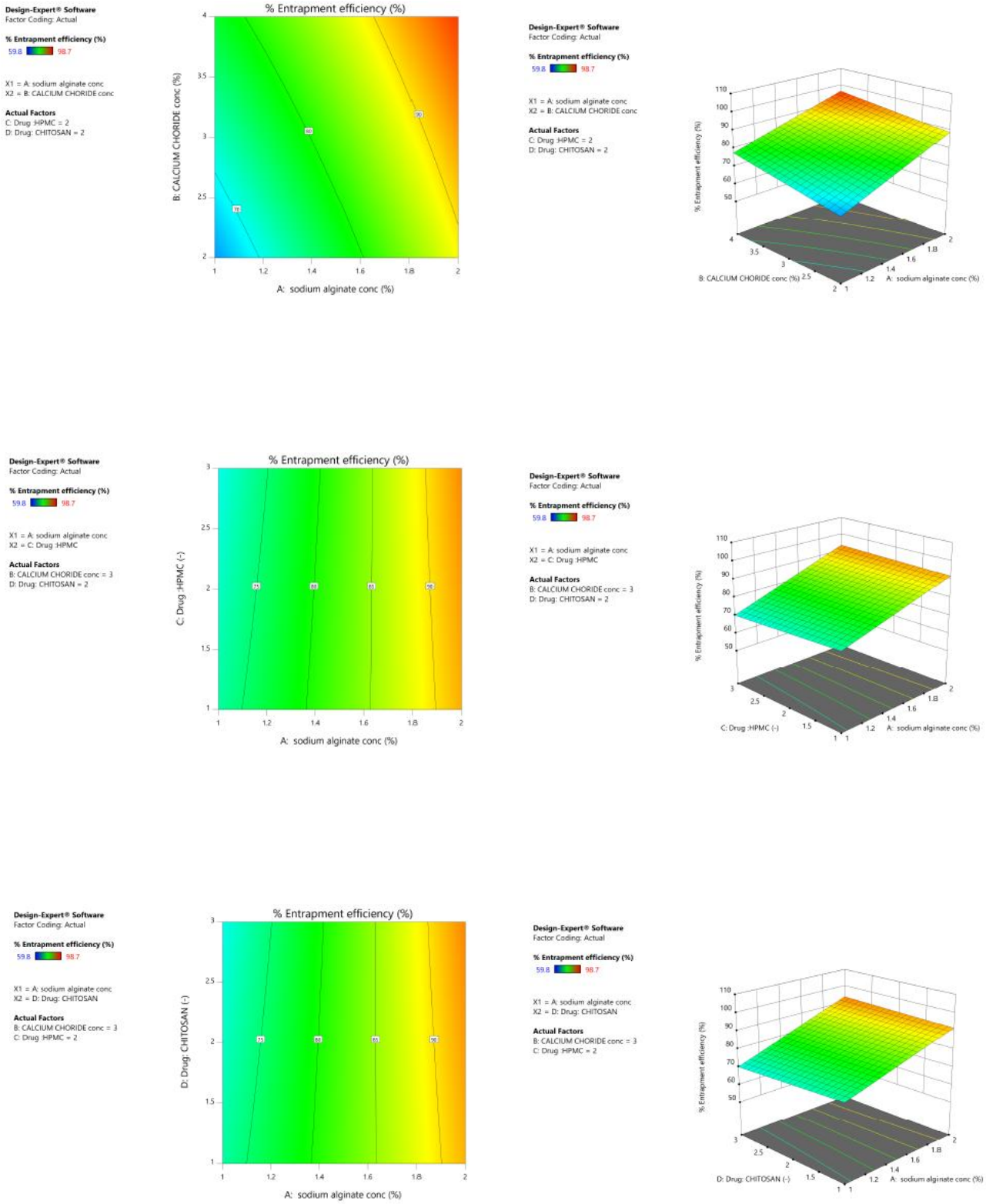

Figure-3: Contour and 3D surface plots of Response-1 (% Entrapment Efficiency)

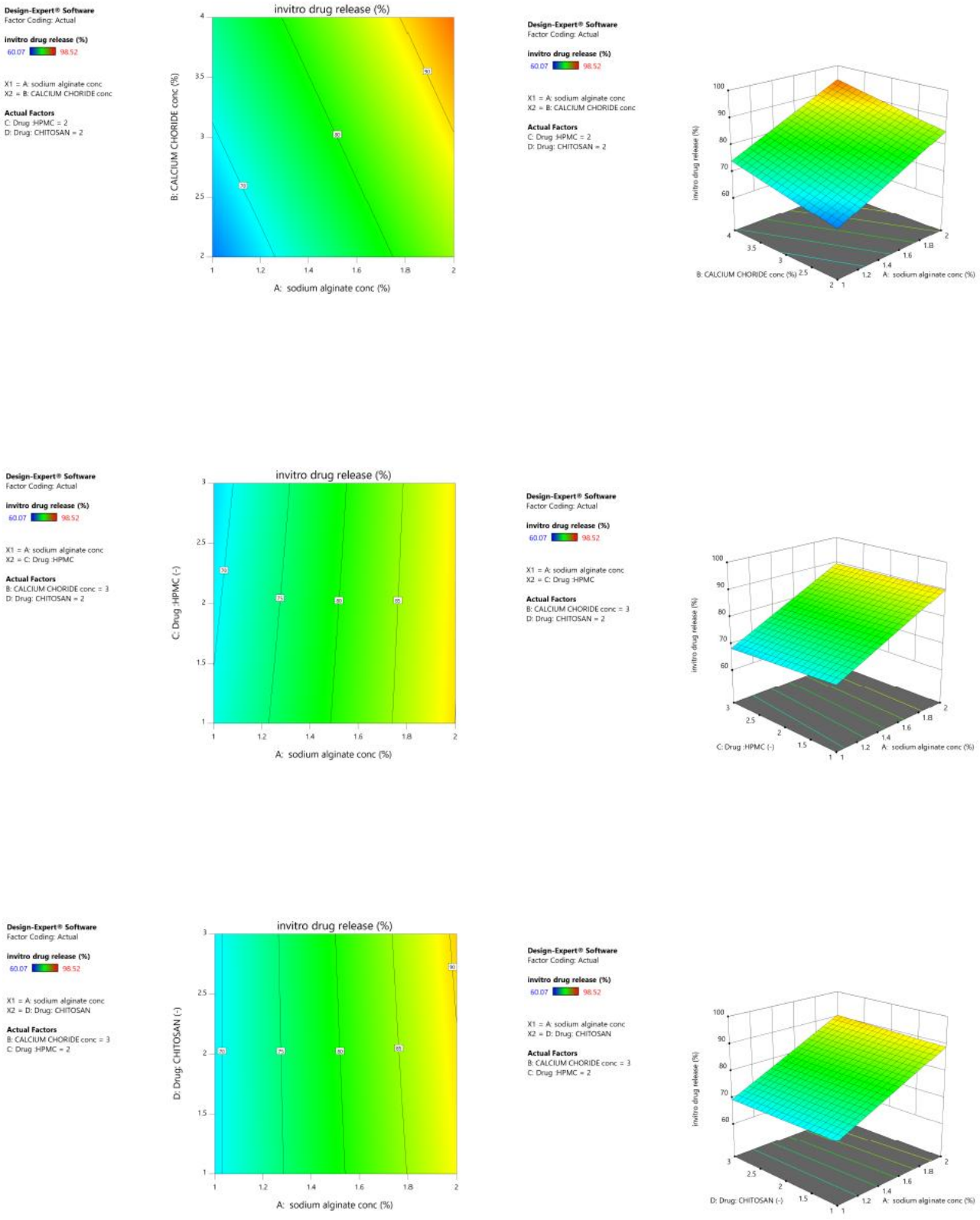

Figure-4: Contour and 3D surface plots of Response-2 (% *In-vitro* Drug Release)

Mathematical modeling of experimental data

Depending on the analysis of the observed values of the responses; a mathematical model for each response was generated and presented in the form of equations.

Quadratic Equation

Quadratic equation indicates the effect of concentration of independent variables on responses i.e., entrapment efficiency and *in-vitro* drug release studies. The positive (+) sign indicates as the concentration of that independent variable increases, the response also increases. The negative (-) sign indicates as the concentration of that independent variable decreases, the response increases.

Quadratic Equation for Entrapment Efficiency

Entrapment efficiency= +82.22+10.51(A) +4.86(B) -0.3713(C) -0.2788(D) -1.11(AB) +1.10 (AC) +1.18(AD)

Quadratic Equation for *In-vitro* Drug Release Studies

In-vitro drug release= +79.60 +10.19(A) +4.72(B) -0.6931(C) +0.3944(D) -0.0169(AB) +0.4319(AC) +0.4294(AD)

(A=Sodium alginate concentration, B=Calcium chloride concentration, C=Drug: HPMC ratio, D=Drug: Chitosan, AB= sodium alginate conc and HPMC conc, AC=Sodium alginate conc and Drug: HPMC, AD=Sodium alginate conc and Drug: Chitosan)

Optimization ofSolid dispersion entrapped alginate beads

The resultant experimental data of all prepared formulations IB_1 to IB_{16} were used to develop an optimized solid dispersion entrapped alginate beads with maximum % Entrapment efficiency and % Drug release by using 2^4 factorial design in design expert software. The suggested optimized formulation has 2% sodium alginate concentration, 4% calcium chloride concentration, 1:1 ratio of drug:HPMC and 1:1 ratio of drug:chitosan. To validate these values, the optimized solid dispersion entrapped alginate beads formulation was prepared and evaluated. The observed responses of this formulation were 90.84% of percentage yield, 61.98% of drug content, 96.23% of entrapment efficiency, particle size of 1173.8 µm and 95.62% of drug release for 12hours as illustrated in Figure-5.

These observed values are in a close agreement with the predicted values. This proved the feasibility of the optimization procedure using factorial design in developing a new ivacaftor solid dispersion entrapped sodium alginate beads formulation with controlled release.

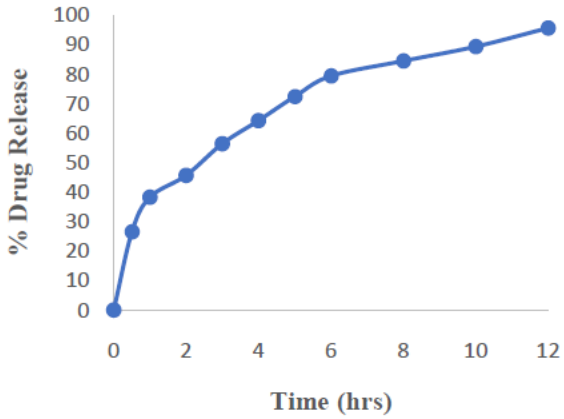

Figure-5: *In-vitro* drug release studies of optimized formulation

3. FTIR studies: The FTIR spectrum of ivacaftor and its formulation are depicted in Figure-6 & 7, it showed N-H stretching at 3332.39 cm^{-1}, O-H stretching at 3155cm^{-1}, C-H stretching at 2957.3 cm^{-1}, aromatic C=C stretch at 1524.45 cm^{-1}, -C=O stretch at 1647.88 cm^{-1} and aryl C-N stretch at 1291.11 cm^{-1}. The ivacaftor solid dispersion entrapped alginate beads formulation showed no major shifting of any functional peaks of drug. Hence it was indicated that there was no interaction between drug and used excipients.

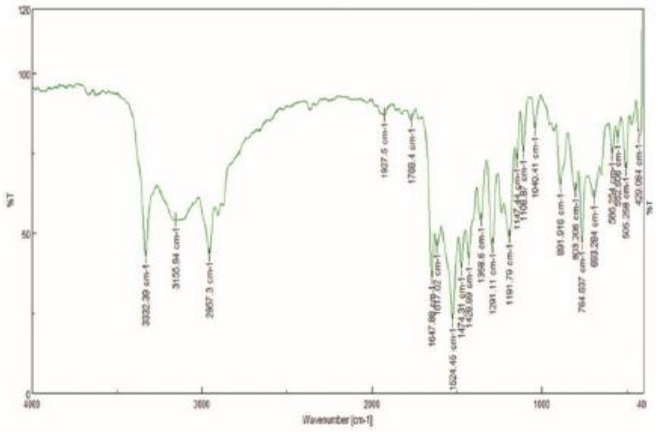

Figure-6: FTIR spectrum of Ivacaftor

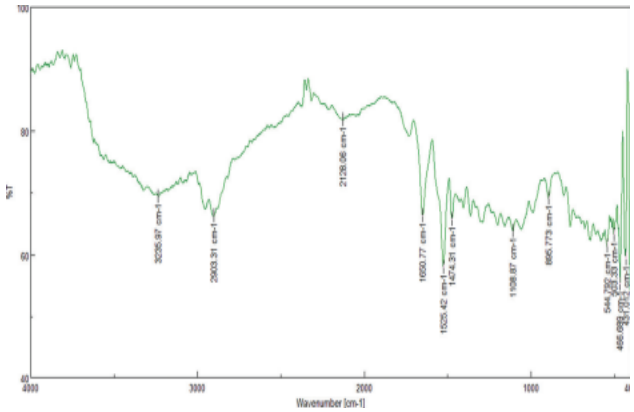

Figure-7: FTIR spectrum of Ivacaftor optimized formulation

4. *In-vitro* drug release kinetics: The *in-vitro* drug release kinetics of optimized formulation followed First order (r^2=0.9831). The obtained value of diffusion exponent (n) is 0.3899, indicating that the release behaviour was by Fickian diffusion.

Ivacaftor is suitable for the development of sustained release formulation. The solubility of ivacaftor was enhanced by preparing into solid dispersions using polyethylene glycol, mannitol and urea as carriers in different ratios by following solvent evaporation method. The solid dispersion containing polyethylene glycol and drug with 1:2 ratio was entrapped into alginate beads by ionotropic gelation method to retain drug in stomach and to prolong the drug release. In beads preparation sodium alginate and calcium chloride were used as gelling and cross linking agents. In present study, the oral sustained release form was developed using Hydroxy propyl methyl cellulose and Chitosan as polymers.

Conclusion

Ivacaftor entrapped solid dispersion entrapped alginate beads were successfully optimized using 2^4 Full factorial design, which gave maximum entrapment efficiency and high drug release for extended period of 12 hrs. The release of ivacaftor was found to follow first order kinetics by Fickian Diffusion. It can be concluded that this method may prove to be a suitable potential option for effective delivery of drug for treatment of cystic fibrosis.

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Conflict of Interest

Nil

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