RESEARCH ARTICLE

Design and Characterization of Hallow Porous Floating Microspheres of Favipiravir

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ABSTRACT

The present investigation deals with the design and characterization of favipiravir floating microspheres for gastro retentive drug delivery system by employing 3^2 factorial design and also to investigate the main effects of different independent variables on microspheres that float. The emulsion solvent diffusion method was used to manufacture floating microspheres with Eudragit S 100 as the polymer. These microspheres will extend the release of the medicine, reducing the frequency of administration and the harmful effects caused by fluctuations in plasma concentration with conventional dosage forms. The main effect of independent variables like polymer Eudragit S 100 concentrations (50, 100, 150 mg) and stirring time (1, 2 and 3 hours) on the performance of microspheres. Formulated microspheres were characterized for responses including drug release, particle size, and entrapment efficiency and floating time. Based on the results of the responses, the optimized composition was arrived using the response surface method graphical and numerical optimization method using design of experiments (DoE) software. Then, the optimized formulation (OFES) was prepared and evaluated for the four responses compared with predicted values to find the validity of the selected model. The optimized formulation was further analyzed for drug-excipient compatibility by fourier-transform infrared (FTIR), differential scanning calorimetry (DSC), and also analyzed by X-ray diffraction (XRD), scanning electron microscope (SEM) analysis. Further zeta potential and micrometric properties were also observed. The results for the formulation FES 1 to 9 found were, that particles size ranged from 0.192 to 0.277 µm, entrapment efficiency ranged from 68.65 ± 1.9 to 76.25 ± 3.2%, percentage drug release range was from 89.25 ± 0.24 to 93.68 ± 0 .25%, and floating time range was from 12 to 23 hours. As per the design, OFES an optimized formulation fitted with the concentration of Eudragit S 100 of 139.1 mg and stirring time of 1-hour. Regarding the kinetic release, the responses were best fitted with Higuchi model of R^2 value of 0.9795 with kinetic mechanism of non-fickian diffusion with R^2 value of 0.9499, indicating good linearity. The combination of different variables and their effects on responses were investigated well using factorial design, and an optimized formulation was developed for favipiravir.

Keywords: Floating microspheres, Favipiravir, Factorial design, DoE, Prolonged release, Eudragit S100.

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INTRODUCTION

Favipiravir is a pyrazine carboxamide derivative, a potent, prodrug, and antiviral agent, which is mostly widely used for the management of COVID-19 of SAR-CoV2, Ebola, polio, measles, and influenza virus.[1] Through endocytosis, the prodrug of favipiravir penetrates the infected cells and undergoes metabolism to become an active drug. Active favipiravir-RTP and viral replication selectively inhibit RNA polymerase and are prevented. Favipiravir-RTP is believed to interact with RNA-dependent RNA polymerase (RdRp) in a variety of ways. RNA polymerase is selectively active favipiravir-RTP inhibits, which also restricts the replication of viral genome.[2] The interaction of favipiravir-RTP with RNA-dependent RNA polymerase is discussed in a variety of theories.[3,4] Favipiravir is a Biopharmaceutical Classification System (BCS) Class II drug that is low-soluble and high-permeable. To overcome drawbacks of conventional dosage forms of Favipiravir like a short half-life as 2 to 5.5, fair absorption at the stomach and increased toxicities like liver dysfunction due to concentration fluctuations. So, to avoid all these limitations, drug is converted into a controlled delivery system by gastro retentive approach.[5] Gastroretentive dosage forms give us novel and significant therapeutic options that extend the gastric residence time. In last few decades,

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several GRDD approaches are designed and developed like high density, low-density floating systems, mucoadhesive systems, swellable systems, super porous hydrogel systems, and magnetic system.[6] Based on all these approaches, a floating system of drug delivery is a promising approach to control the release and rate of drugs in GIT.[7] Floating microspheres are multi-unit dosage form and non-effervescent approach. The single-unit floating systems have the disadvantages of non-reproducibility, increased dose dumping and unreliable in prolonging the gastric residence time; thus in the present study drug is converted into a multi-unit dosage form.[8] Microspheres are tiny in the micrometer range, spherical particles between 1 to 1000 µm. Eudragit (methacrylate copolymers) have recently drawn more interest for the preparation of modified dosage forms due to their inertness, solubility, and generally low toxicity.[9-11] Using an emulsion solvent diffusion approach, multi-unit floating microspheres were created using acrylic polymer. Drug release can be modified by changing the polymer-to-drug ratio[12] and floating can be achieved throughout the upper portion of the stomach and remain there for long time against the movement of their peristalsis.[13-17]

This study aimed to develop microspheres containing the antiviral medication favipiravir and the polymer Eudragit S 100 for use in COVID-19. A 3^2 factorial design was used to evaluate the performance of the floating microspheres, with two independent factors at three levels each. Analyzed the favipiravir floating microspheres for a number of parameters, including drug release percentage, particle size, entrapment efficiency, and floating time. Through the use of DoE software, graphical optimization methods, numerical optimization, and response surface analysis were employed to evaluate the optimized formulation. Studies on the optimized formulation were also conducted on drug-excipient compatibility, scanning electron microscopy (SEM), and X-ray diffraction (XRD).[18-20] This research is unique in that it is the first of its kind to create a floating microsphere-based controlled-release drug delivery system for favipiravir. This will increase patient compliance by lowering the frequency of administration, which in turn reduces toxicities caused by variations in plasma concentration of favipiravir.[21]

MATERIALS AND METHODS

A comprehensive description of the material and methods portion is provided below.

Materials

A supply of favipiravir was provided by VAREN Life Sciences, Hyderabad (Telangana, India). Polymers Eudragit S 100 and Eudragit L 100, HPMCK and ethylcellulose were purchased from Yarrow Chemicals Pvt. Ltd, Bombay (Maharashtra, India). Methanol, polyvinyl alcohol and dichloromethane were obtained from SD fine chemicals.

Experimental Design

The composition of the nine favipiravir floating microsphere formulations was determined using the Design Expert Software, version 22.0.6.0, by Easy Inc., Minneapolis, MN, USA, and a 3^2 complete factorial design. In order to manipulate the independent variables, namely polymer Eudragit S 100 concentration and stirring duration, three levels were used: low [-1], medium [0], and high.[1] as shown in Table 1. The researcher has chosen the particle size, percentage of drug entrapment efficiency (EE%), percentage drug release (%DR), and floating time as dependent variables.[22]

Preparation of Favipiravir-loaded Floating Microspheres

The method of emulsion solvent diffusion was used to prepare floating microspheres. Accurately weighed polymer Eudragit S 100 was dissolved in a 1:1 ratio of ethanol to dichloromethane. A definite weight of favipiravir (200 mg) was dispersed above the polymer solution and stirred using a sonicator. Slowly adding 1% PVA dropwise using a syringe needle, the resulting drug dispersion was emulsified using a magnetic stirrer set to 1000 rpm for varying stirring durations. Filtration was used to collect the formed microspheres, which were subsequently washed with water and allowed to dry at room temperature.[23,24] Table 2 comprises the composition of different Favipiravir floating microspheres prepared.

Characterization of Favipiravir Floating Microspheres

The nine formulations of favipiravir floating microspheres were prepared by using Design Expert Software, version 22.0.6.0 and responses like particle size, percentage of drug entrapment efficiency (EE%), percentage drug release (%DR), and floating time were selected as dependent parameters. The responses were analyzed using Experimental design software to obtain optimized values using the response surface method, overlay plot etc. The optimized batch subject was characterized by studies like fourier-transform infrared (FTIR), differential scanning calorimetry (DSC), XRD, micrometric studies, zeta potential, and drug release kinetics.

Particle size analysis

A Malvern particle size analyzer (Malvern Mastersizer 2000 instruments Ltd., UK) was used to determine the average microsphere size. In a glass beaker, 5 mg of each sample was mixed with 500 mL of double-distilled water while being gently stirred at 600 rpm. Every measurement was made in triplicate using the mean ± SD.[25-27]

Drug entrapment efficiency

About 50 mg of microspheres were accurately weighed, mixed with 10 mL of ethanol in a 100 mL volumetric flask, and then filled with 0.1 N HCl to bring it to the final volume. Dissolved solution was filtered using whatsman filter paper No. 44 and then filtrate was diluted appropriately to determine its absorbance under UV spectrophotometer.[28,29] The percentage drug entrapment was calculated using the drug's standard plot.

Table 1: Variable scope and intensity in experiments

S. No	*Variables*	*Actual and coded values*		
		-1	*0*	*1*
1	ES 100 [mg]	50	100	150
2	Stirring time [hours]	1	2	3

Table 2: Composition of favipiravir floating microspheres

Composition	*FES 1*	*FES 2*	*FES 3*	*FES 4*	*FES 5*	*FES 6*	*FES 7*	*FES 8*	*FES 9*
Stirring time [hours]	2	2	2	1	1	1	3	3	3
Favipiravir [mg]	200	200	200	200	200	200	200	200	200
Eudragit S 100 [mg]	50	150	100	50	150	100	50	150	100
HPMC K 100 [mg]	100	100	100	100	100	100	100	100	100
Ethyl cellulose [mg]	750	750	750	750	750	750	750	750	750
Methanol [mL]	25	25	25	25	25	25	25	25	25
DCM [mL]	25	25	25	25	25	25	25	25	25
PVA 1% [mL]	100	100	100	100	100	100	100	100	100

Diffusion investigations in-vitro

Drug release studies were conducted *in-vitro* with the Franz diffusion cell. About ten mg of floating microspheres were placed in donor cells. The receptor compartment contained 200 mL of 0.1N HCl and was stirred by employing a magnetic stirrer at 100 rpm. Between the donor and receiver, a dialysis membrane was set up. In order to maintain sink conditions, 1-mL aliquots of the sample taken were replenished regularly with an equal volume of diffusion medium. This allowed us to quantify the percentage of drug release at different time points for all formulations using standard formulas, as the samples were withdrawn at varied dates.[30,31]

Floating time

The duration of floating was used to calculate the buoyancy in the beaker. About 100 mg of floating microspheres were added to 300 mL of 0.1 N HCI stirring at a paddle speed of 100 rpm. Calculated the time microspheres took to reach the surface and the time the microspheres floated for after that was calculated using simple visual observation.[28-31]

Experimental Design

There were nine different formulations made using a 3^2-full factorial design, with each formulation being optimized for three combinations of two independent variables or factors: polymer concentration (X1) and stirring time (X2). The experimental response, Y, the mathematical mean response, b, the predicted factor X1 coefficient and the interaction times, X1 and X2, are all found in polynomial equations. The results of four selected responses (Table 3) were analyzed using software to obtain optimized values for X1 and X2 using the response surface method, overlay plot etc.

Following this, the optimized formulation (OFES) was created and defined for each of the four answers using the same methods. This allowed us to compare it to the projected values and ensure that the design was valid for the production of the microspheres that are used today. The OFES was further analyzed for drug excipient compatibility studies by FTIR, DSC, stability studies, zeta potential, and surface morphology by SEM analysis and XRD studies.

FTIR analysis

The infrared spectra of the drug and OFES was obtained using the potassium bromide dispersion procedure with the aid of a FTIR equipment (Bruker) to determine the compatibility between the drug and excipients. One mg of the sample was mixed with 100 milligrams of potassium bromide to create a disc. After that, the disc was put in a Bruker FTIR spectrophotometer's sample beam, and spectra in the 400 to 4000 cm^{-1} range.[21]

DSC study

During DSC, a sample is either heated, cooled, or kept at a constant temperature, and the amount of heat energy received or emitted is recorded. Mettler Toledo DSC 822e device was used for pure drug and OFES. Samples were heated at 100°C/min in nitrogen in tared aluminum pans that had been sealed after being accurately weighed.[32,33] Then, DSC spectra were recorded.

XRD study

The X-ray powder diffractometer is a very effective and well-respected method for analyzing the structure of materials. This has the ability to reveal details about the atomic structure of the crystalline material. Here, the diffraction experiments were conducted with the Bruker AXS D8 Advance diffractometer[34,35] for samples of pure drug and OFES.

Zeta potential

The overall charge of a particle and its stability in a certain formulation are both depicted by its zeta potential. In order to find the zeta potential using the differential light scattering method, the Zeta sizer Nano-ZS90, made by Malvern Instrument Ltd. of the United Kingdom, was used. Samples of microspheres (OFES) were dispersed again in Milli-Q water. At 25°C, triplicates of each measurement were performed.[36,37]

Micrometric studies

Using conventional procedures, the manufactured OFES microspheres were evaluated for flow characteristics such as bulk density, tapped density, Carr's or compressibility index, angle of repose, and Hausner's ratio.[39-43]

SEM analysis

A sample of OFES was examined using an SEM (JEOL, JSM 50A, Tokyo, Japan). In order to secure the tape, a double-sided tape and razor blade is used, and a proper number of microspheres were adhered to the metal (aluminum) stubs and broken. For the secondary electron emissive SEM, a gold/

palladium sputter coating was applied for 120 seconds at 14 mA in an argon environment. At an acceleration voltage of 15 KV, the morphology was observed[37,38] and captured.

RESULTS AND DISCUSSION

The results of four selected dependent parameters (responses) determined are shown in Table 3. These results are further analyzed by DoE software using response surface methodology, which elucidated their corresponding contour and response surface plots as shown in Figures 1 and 2.

The contour, response surface plots (Figure 1–2), illustrated the influence of the retarding agent and stirring time on four selected responses. These illustrations are also exhibited in polynomial equations shown in Table 4

Particle Size (Y1)

Table 3 shows the particle size [Y1] of all prepared floating microspheres between 0.1 and 0.5 µm. The average particle size range was between 0.137 ± 0.01 µm and 0.277 ± 0.07 µm. Eudragit S 100 concentration [X1] exhibited a negative relationship with PS, indicating the antagonistic effect of Eudragit and particle size. As the concentration of Eudragit S 100 increased the particle size was decreased may be due to more crenulation or shrinkage of a sphere on drying, which supports the increased floating duration upon absorption of more moisture when added to the fluid. Stirring time [X2] exhibited a positive relationship with particle size, indicating a synergistic effect. As stirring time increased, the particle size also increased due to particle aggregation during long stirring times. The interaction effects of X1 and X2 shown a positive relationship with particle size. But the multiple effects of X1, X2, i.e., at increased to double time, showed a negative relationship with particle size as well as with the X2. The impact of X1 and $X1^2$ is more than X2 and $X2^2$ on particle size as co-efficient of X1 (0.0238) is greater than co-efficient of X2 (0.0018)

Entrapment Efficiency [Y2]

%EE of all formulations of FESs was from 68.65 ± 1.9 to 76.25 ± 3.2%. Eudragit S 100 concentration [X1] exhibited a positive relationship with %EE, indicating the synergistic effect. As polymer concentration increased the %EE was also increased due to increased accommodation of drug with higher polymer

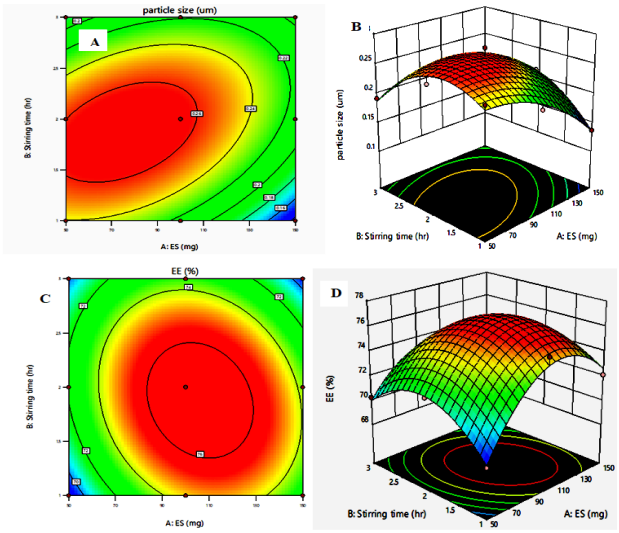


Figure 1: Contour plots for [A] PS , [B] EE% with their corresponding response surface plots

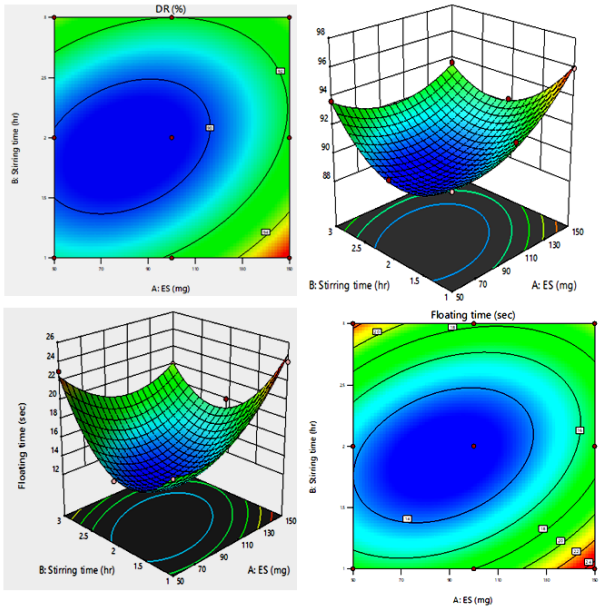


Figure 2: Contour plots for (C) DR% and (D) floating time with their corresponding response surface plots

Table 3: Results of the floating microspheres of favipiravir

Formulation code	*Particle size [Y1] µm*	*EE [Y2] %*	*DR [Y3] %*	*Floating time [Y4] hours*
FES1	0.212 ± 0.02	74.24 ± 1.3	92.32 ± 1.13	18 ± 1.21
FES2	0.215 ± 0.06	73.18 ± 1.6	91.86 ± 1.36	18 ± 1.15
FES3	0.192 ± 0.05	70.25 ± 2.24	93.68 ± 1.25	23 ± 1.13
FES4	0.206 ± 0.008	75.12 ± 2.69	92.55 ± 1.36	19 ± 1.21
FES5	0.247 ± 0.02	72.02 ± 3.6	90.02 ± 1.25	14 ± 1.31
FES6	0.277 ± 0.01	76.25 ± 3.2	89.25 ± 1.24	12 ± 0.93
FES7	0.137 ± 0.01	72.12 ± 2.3	95.95 ± 1.25	24 ± 0.32
FES8	0.194 ± 0.03	69.31 ± 1.6	93.63 ± 1.36	20 ± 1.11
FES9	0.247 ± 0.02	68.65 ± 1.9	91.23 ± 1.27	17 ± 1.17

*all the values are given in mean ± SD

Table 4: Factorial design proposed polynomial equations for responses

Particle Size [Y1] = +0.2639-0.0238 X1+0.0018 X2 +0.0280 X1X2-0.0278 $X1^2$ -0.0468 $X2^2$
Entrapment Efficiency% [Y2] = +76.67+0.7917 X1 -0.5250 X2 -1.10 X1X2-3.75 $X1^2$ -2.79 $X2^2$
DR %[Y3] = +89.47+1.16 X1 -0.0933 X2 -1.19 X1X2 + 1.59 $X1^2$ + 2.62 $X2^2$
Floating time [Y4] = +12.67+1.33 X1 +0.1667 X2 -2.5 X1X2+ 3.00 $X1^2$ + 5.50 $X2^2$

content. Increase in stirring time (X2), the %EE was decreased may be due to diffusion of drug back on excess duration of stirring. The interactive effects between X1 and X2, as well as multiple effects of X12 and X22, have shown a negative relationship with %EE. The influence of X1 and $X1^2$ is more than X2 and $X2^2$ on %EE as co-efficient of X1 (0.7917) is greater than co-efficient of X2 (0.525)

%Drug Release

The %DR of all formulations of FESs was 89.25 ± 0.24 to 93.68 ± 0.25%. in 12 hours (Figure 3). The drug release was prolonged up to 12 hours for all formulations. The minimum floating time was observed for 12 hours (FES6) and the release was maximum extended to 12 hours, which demonstrated that the %DR was not significantly increased with an increase in floating time even though for 24 hours. As 90% of the drug was released in 12 hours only, it indicated that the ability of selected polymers at tested concentrations in the present investigation are not sufficient to retard the release upto 24 hours.

Eudragit S 100 concentration [X1] exhibited a positive relationship with %DR, indicating that the synergistic effect may be due to an increased %EE at higher concentrations of polymer. Stirring time [X2] shown a negative relationship with %DR indicated the antagonistic effect may be due to decreased %EE at higher stirring times. The interactive effects between X1 and X2 showed a negative relationship with %DR. However, the multiple effects of X12 and X22 showed a positive effect that indicating the synergistic effect. The influence of X1 is more than X2 on %DR as co-efficient of X1 (1.16) is greater than co-efficient of X2 (0.0933)

Floating Time

The Floating time of all formulations of FES s was ranged from 12 to 23 hours. Eudragit S 100 concentration [X1] exhibited a positive relationship with floating time, indicating the synergistic effect. It demonstrated that the increased ES100 concentration increased the floating duration may be due to the increased capacity of microspheres to be floated for long time at higher concentrations. As stirring time [X2] increased, the floating time also increased, indicating the synergistic effect may be due to the formation of a continuous film on surface without interruptions at long-time stirring. The interactive effects are between X1 and X2 shown a negative relationship with %DR. But, the multiple effects of $X1^2$, $X2^2$ shown a positive effect indicating that synergistic effect. The effect of X1 is found more than X2 on floating time as co efficient of X1 (1.33) is greater than co-efficient of X2 (0.1667).

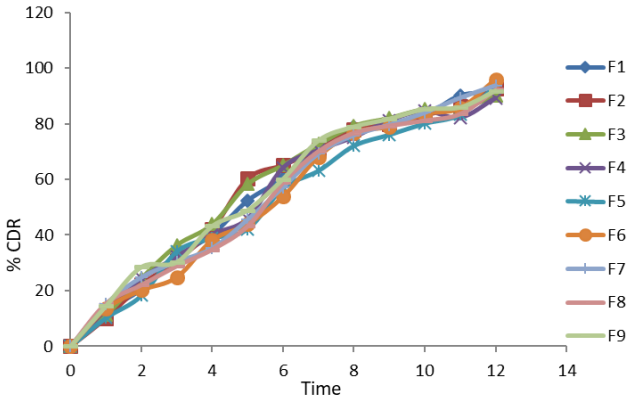


Figure 3: *In-vitro* release data of FES1 to FES9

It is based on the Design Expert Software [v 22.0.6.0] from Stat-Ease, Inc., Minneapolis, MN, USA. It was used for this study, data obtained from all formulations were analysed using 3^2 full factorial designs. The software was then polynomial models, response variables and study design are generated using this tool. Additionally, the data was analyzed using ANOVA which, which significantly impacted the coefficients of the response regression. The software was also used to calculate the F and P test results. A software programme developed an overview of the model's significance for all responses (Y1-Y4). The model proposed the quadratic for all four responses and is significant for all as shown in Table 4. The ANOVA findings showed that the models for the analysed responses (Y1-Y4) were significant (p 0.05) (Table 5) and study also confirmed the influence of X1 is greater than X2 on all selected four responses.

An improved formulation for floating favipiravir microspheres with desirable effects was created using the desirability technique and graphical optimization (Figures 4 and 5). Values from the chosen experiment were quantitatively compared with the projected values to ensure its validity (Table 6). It shows the model is valid for the successful design of favipiravir microspheres as the %prediction error for all responses is below 10%.

Drug-Excipient Compatibility Study

Drug-excipient compatibility studies are a crucial component of the formulation process for the creation of all types of

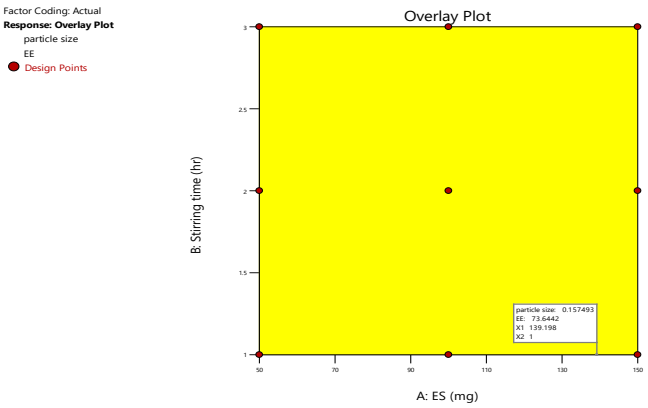


Figure 4: Overlay plot of FES showing optimized composition

Table 5: Model selection using factorial design expert

Particle size						
Model type	*p-value*	*R2*	*AdjustedR²*	*Predicted R²*	*PRESS*	*Remarks*
Linear	0.0400	0.2631	0.0175	-0.7278	0.0225	
2FI	0.0360	0.5038	0.2061	-1.0462	0.0267	
Quadratic	0.0133	0.9594	0.8918	0.6466	0.0046	Suggested
Cubic	0.0197	0.9703	0.7625	-4.4103	0.0705	
%Entrapment Efficiency						
Modeltype	*p-value*	*R2*	*Adjusted R²*	*Predicted R²*	*PRESS*	*Remarks*
Linear	2.86	0.0991	-0.2012	-1.1681	118.48	
2FI	2.98	0.1880	-0.2991	-3.7295	258.46	
Quadratic	0.6575	0.9763	0.9367	0.7453	13.92	Suggested
Cubic	0.6317	0.9927	0.9416	-0.3307	72.72	
%Drug release						
Modeltype	*p-value*	*R2*	*AdjustedR²*	*PredictedR²*	*PRESS*	*Remarks*
Linear	2.03	0.2477	-0.0030	-0.7834	58.66	
2FI	1.95	0.4207	0.0731	-1.8831	94.83	
Quadratic	0.3176	0.9908	0.9755	0.9040	3.16	Suggested
Cubic	0.3350	0.9966	0.9727	0.3782	20.45	
Floating Time						
Model type	*p-value*	*R2*	*Adjusted R²*	*PredictedR²*	*PRESS*	*Remarks*
Linear	4.23	0.0918	-0.2109	-1.1288	251.20	
2FI	4.05	0.3037	-0.1141	-2.2995	389.34	
Quadratic	1.11	0.9689	0.9171	0.6614	39.95	Suggested
Cubic	1.0000	0.9915	0.9322	-0.5445	182.25	

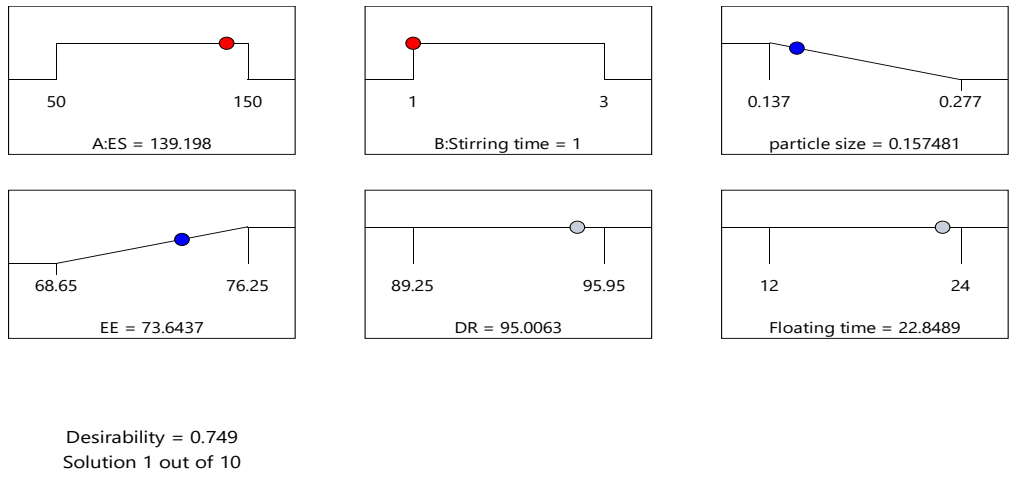


Figure 5: Desirability graphs

Table 6: Validation of optimized formulation

Optimized formulation	*X1: Eudragit S 100 (gm.)*	*X2; Stirring time (hr.)*	*Responses*	*Predicted values*	*Experimental values (Mean±SD)*
OFES	139.20	1.00	Y1 Particle size (µm)	0.157	0.137±0.04
			Y2 EE (%)	73.64	72±1.5
			Y3DR (%)	95.006	95.95±1.2
			Y4 Floating time (hr)	22.85	24±0.15.

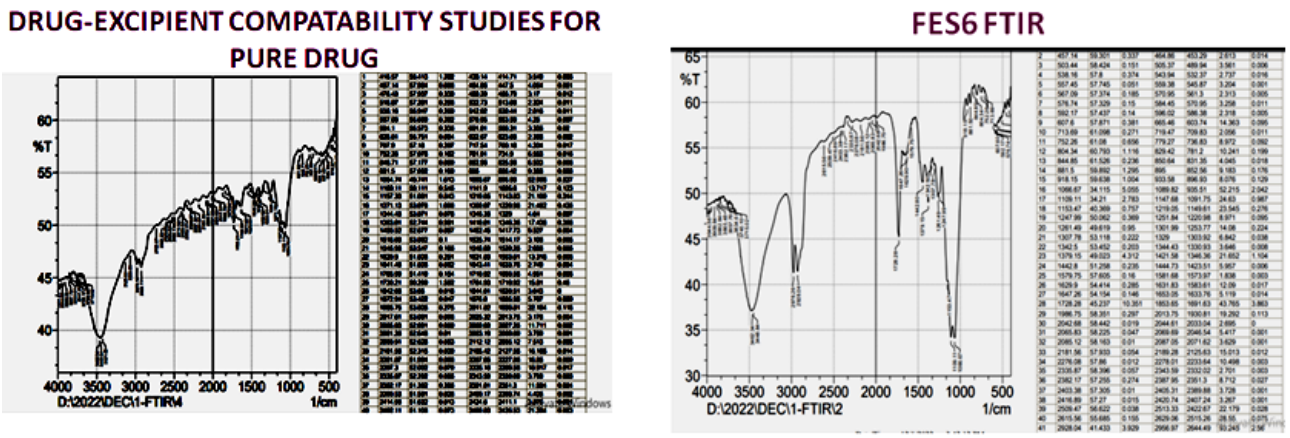


Figure 6: FTIR spectra

medication. Drug-excipient interactions can impact the chemical composition, stability, and bioavailability. Drug-excipient compatibility can be assessed using many techniques, including DSC, FTIR, and XRD. FTIR is a straightforward method that yields data regarding the chemical reactions occurring between the active pharmaceutical ingredient (API) and the excipient. This information assists formulators in identifying chemical groups to intentionally exclude from the excipients, hence enhancing the stability of the blends.

FTIR

To identify potential drug-excipient interactions, infrared spectra were taken of the pure drug and the blend of the core components with drug of the optimized batch (OFES) as shown in Figure 6 to find the drug excipients compatibility. The pure form of favipiravir drug and an optimized formulation of floating microspheres (OFES) revealed characteristic spectral peaks. Specifically, the C-C stretching vibration was observed at a wavenumber of 1466.29 cm^{-1}, whereas amine stretching of Favipiravir was detected at a wavenumber of 3345.95 cm^{-1}, while stretching of C=O observed at 1657.83 cm^{-1}. C = C stretching was found at 1466.29 cm^{-1} and the C-F stretching occurred at 1178.02 cm^{-1}. The optimized formulation exhibited characteristic bands at 3354.27 cm^{-1} for amine stretching, stretch for C = O is 1687.18 cm^{-1}, the stretch for C = C 1440.79 cm^{-1}, and the stretch for C-F is 1186.42 cm^{-1}. Results of FTIR studies revealed that there were no extra peaks observed in OFES when compared with pure drug, which indicated that physical and chemical compatibility between the pure drug and excipients.

DSC study

Figures 7 and 8 show the DSC thermograms of pure drug of favipiravir and OFES microspheres formulations. An endothermic peak was found at 195.63º which represents the melting point of drug in both indicating that the same thermal behavior was exhibited by pure drug and OFES microsphere formulation, It further confirmed that there was no interaction between the pure drug and the excipients

SEM analysis

The OFES surface morphology and surface texture image (Figure 9) revealed that the morphology of OFES was spherical, distant, rough, hollow, and porous surface. The surface of microspheres observed as porous indicated the chances of increased floating properties.[42]

X-ray diffraction study

A powerful technique for analyzing crystalline materials' structural properties is X-ray diffraction (XRD), which

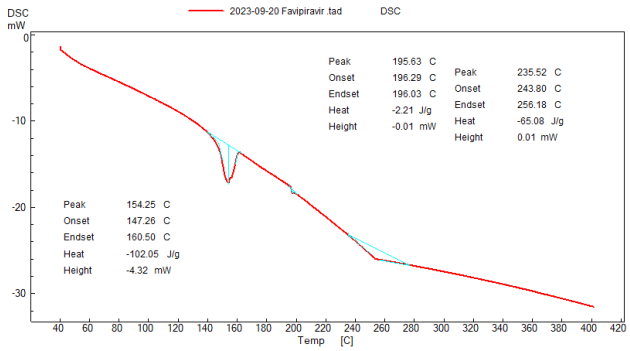


Figure 7: DSC of favipiravir pure drug

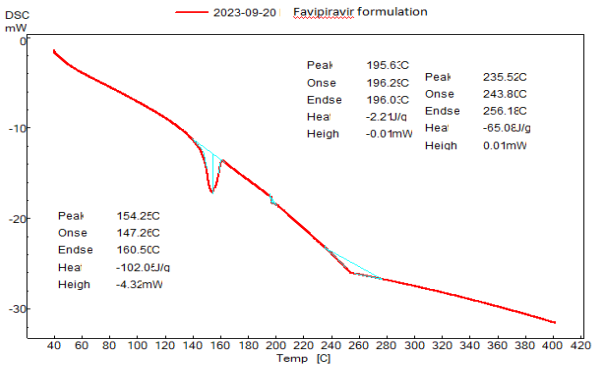


Figure 8: DSC thermogram of favipiravir microspheres formulation (OFES)

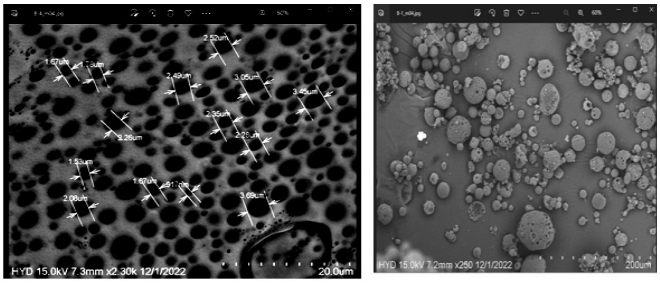


Figure 9: SEM images of OFES microspheres

encompasses the determination of atomic arrangement, crystallite dimensions, and the presence of defects or faults. The very less intense XRD peaks of OFES (Figure 10) revealed that the amorphous nature of microspheres confirmed the dispersion of favipiravir at the molecular level.[42]

Zeta Potential

Zeta potential was observed between the 30 to 48 mV range, as represented in Figure 11, with a polydispersity index between 0.378 to 0.467. These observations indicated that moderate zeta potential charged particles possess a greater stability.

Micromeritic Properties

Bulk density of OFES was found to be 0.368 ± 0.03. Tapped density was 0.485 ± 0.01, compressibility index or carr's index was found to be 12.24 ± 0.1, Hausner's ratio was 1.15 ± 0.25 and angle of repose was found to be 24.18 ± 0.23°C. From above observations, the densities of floating microspheres (OFES) were found to be less than the density of gastric fluid, which leads to float over gastric fluid and excellent flow properties.[39-44]

Release Kinetic Study

OFES formulation was subjected to *in-vitro* drug release kinetics, by applying zero-oder, first-order, Higuchi, and Korsmeyer peppas models and their plots are shown in Figure 12 and values are given in Table 7. The R^2 value of zero order kinetics was 0.979, which is higher when compared to the R^2 value of first order, indicating the zero-order rate of drug

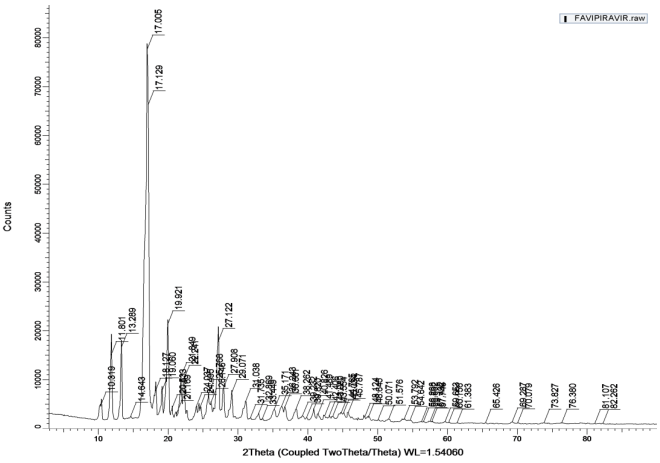
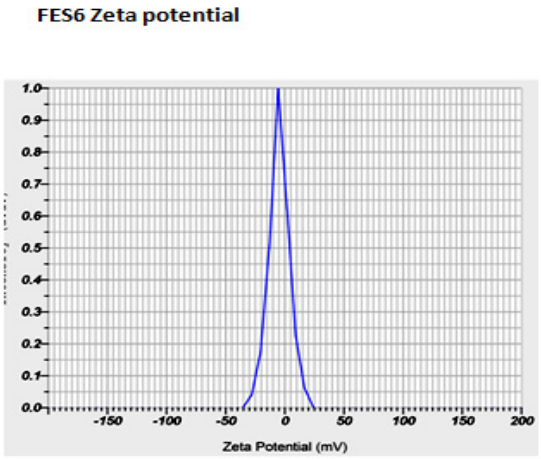


Figure 10: XRD of favipiravir microspheres formulation (OFES)



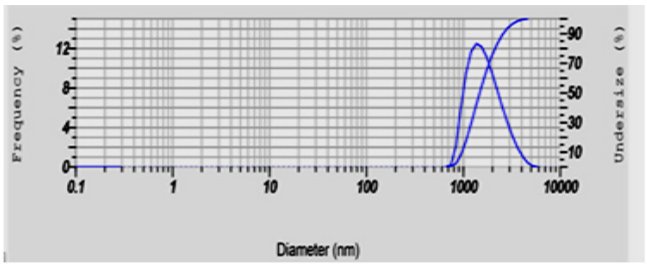


Figure 11: Zeta potential and PDI of OFES

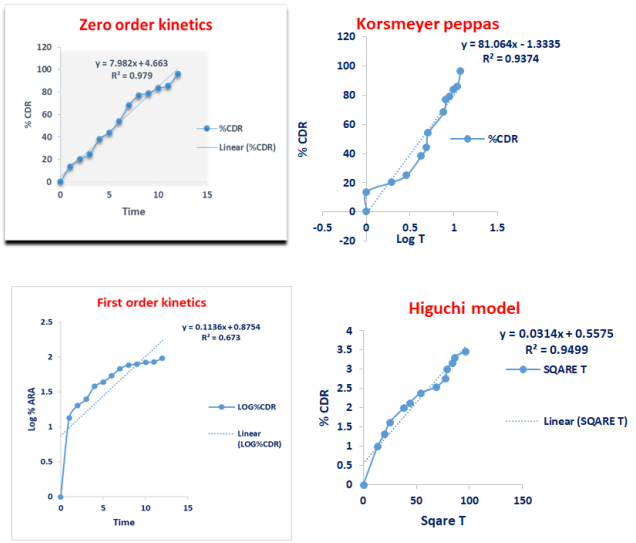


Figure 12: *In-vitro* drug release kinetics

release from prepared microspheres. Higuchi and Korsmeyer peppas models assessed the drug release mechanism for favipiravir. OFES followed a good linearity with a regression coefficient of $R^2 = 0.949$ in Higuchi model indicating optimized formulation released drug by diffusion mechanism in a controlled manner.

Table 7: Drug release kinetics

Time (hrs)	*%CDR*	*SQARE T*	*LOG T*	*LOG%CDR*	*ARA*	*LOG%ARA*
0	0	0	0	0	0	0
1	13.52	1	0	1.13097669	86.48	1.93691568
2	20.18	1.32458	0.29103	1.30492116	79.82	1.90211172
3	24.85	1.62205	0.45712	1.39532639	75.15	1.87592898
4	38.15	2	0.62689	1.58149454	61.85	1.7913397
5	43.89	2.13605	0.68954	1.64236558	56.11	1.74904027
6	53.84	2.38462	0.70815	1.73110505	46.16	1.6642658
7	68.15	2.53914	0.88502	1.83346586	31.85	1.50310944
8	76.82	2.75942	0.91031	1.8854743	23.18	1.36511343
9	78.89	3	0.954243	1.89702196	21.11	1.32448823
10	83.47	3.162278	1	1.92153041	16.57	1.21932251
11	85.58	3.316622	1.041393	1.93237228	14.42	1.15896526
12	95.95	3.464102	1.079181	1.98204498	4.05	0.60745502

CONCLUSION

The study investigated the design and characterization of favipiravir floating microspheres, a potential gastroretentive drug delivery system using 3^2 factorial designs. Eudragit S 100 polymer was used to prepare microspheres using the emulsion solvent diffusion method. The optimized formulation OFES showed the best results, with particle size (0.137 µm), entrapment efficiency (72%), drug release (95.95%), and floating time (24 hours). Based on the experiment, the polydispersity index was 0.454 and the zeta-potential was 38.7 mV with a spherical rough, porous surface. The formulated preparation adheres to the zero-order and Higuchi release models. FTIR and DSC studies also confirmed the good compatibility between drug and excipients. From the present results, it can be concluded that favipiravir-loaded floating microspheres were first time successfully designed for the prolonged release of drug using ES 100 for reduction of dose frequency and dose of a drug to use in the treatment of viral diseases.

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