INTRODUCTION

Itraconazole incompletely absorbed from the gastrointestinal tract. It is well absorbed from the upper part of GIT, possibly due to a weak basic property having ionization constant (PKa) 3.7 and is highly lipophilic [1, 2]. This narrow absorption window is responsible for its low bioavailability, unpredictable absorption and inter and intrasubject variability [3]. The plasma drug concentration should be above minimum effective concentration for desired pharmacological action. In the case of immuno-compromised patients the plasma concentration lower then minimum effective concentration may results in a relapse of disease due to poor therapeutic effect [4]. Several attempts have been made to improve the oral bioavailability of itraconazole such as floating gastroretentive tablets [5], mucoadhesive sustained-release tablet by compression of solid dispersion [6], self-emulsifying formulation [7], solid dispersion [8], mixed polymeric micellar formulation [9].

Itraconazole has a narrow absorption window in the upper gastrointestinal tract which represents a rationale to develop a gastroretentive dosage form to provide continuous delivery of drug at its absorption site. To increase the absorption of the drug, it is very important to know the absorption site of drug. Various gastroretentive formulations have been studied in last few decades such as bioadhesive systems; floatation systems; high-density systems; magnetic systems; swellable systems; and super porous hydrogel systems to prolong the stomach retention of the dosage form. The floating dosage forms are the most reliable and economical among several approaches to increase the gastric residence time and design of experiment approach was evaluated for particle size, entrapment efficiency, in vitro floating ability and drug release characteristics.

RESULTS: The physicochemical analysis was done to confirm any interaction between drug and excipients. The Scanning Electron Microscopy (SEM) showed a smooth, spherical surface with an inner hollow cavity. The stability study proves that the hollow microspheres were more stable under different storage conditions with no significant changes in formulation. The drug release mechanism of the optimized batch can be explained by Korsmeyer Peppas model.

Conclusion: Based on the results, the hollow microspheres with a release modifying polymer offers a superior approach to retain the formulation in the stomach.

Keywords: Floating hollow microspheres, Itraconazole, Stomach specific delivery

MATERIALS AND METHODS

Materials

Itraconazole was received as a gift sample from Zydus Cadila Healthcare Limited, India. Eudragit E100 was received as a gift sample from Evonik Degussa India Pvt. Ltd, Mumbai, India. Ethyl Cellulose, Dichloromethane, Polyvinyl alcohol (PVA) and Tween 80 were purchased from Thomas baker Pvt. Ltd., New Delhi. All other reagents and solvents used were of analytical grade and used without further modification.

Process conditions for floating microspheres

Hollow microspheres were prepared by using the emulsion solvent diffusion evaporation method with slight modification from previously reported methods [20-22]. Ethylcellulose was used as low-density matrix-forming polymer and Eudragit E100 was used as release modifying polymer. Dichloromethane and ethanol were used as an organic solvent and PVA solution in distilled water was used as an aqueous surfactant phase. The investigated process variables that may affect the microsphere preparation, including temperature (room temperature, 40, 60), stirring speed (250 and 300 rpm), and...
stirring time (30 min, 1 h, and 2 h). The Floating microsphere preparation describes in the following text.

Preparation of microspheres

The non-effervescent hollow microspheres containing itraconazole were prepared by using the above-mentioned method. Drug, ethylcellulose and Eudragit E100 were co-dissolved in dichloromethane and ethanol mixture (1:1). The resultant slurry was then introduced slowly in a drop-by-drop manner to 30 ml PVA solution containing 0.2% w/v Tween-80 while being stirred at 350 rpm using a three-blade propeller-type agitator for 2 h at 40 °C. The polymeric floating microspheres were formed by diffusion and subsequent evaporation of solvent mixture. The system temperature was maintained constant throughout the process to evaporate the solvent. The formed microspheres were harvested by filtration and washed three times with distilled water. The collected hollow microspheres were dried at room temperature for 24 h and stored in desiccator [23, 24].

Design of experiment

A central composite design was applied to design the experiment to optimize the responses and optimum process parameters. The Polymers ratio (X1) and concentration of PVA (X2) were selected as independent variables, whereas particle size (R1), drug entrapment efficiency (R2), percentage buoyancy (R3) and percent cumulative drug release (R4) were kept as dependent variables. Each factor was studied at 3 levels (-1, 0, +1); the experimental design layout suggested thirteen runs. Statistical analysis was performed and polynomial equations for each response variable was generated using Design-Expert software® (Version 11.0.0.5, Stat-ease Inc., Minneapolis, MN). The design matrix including investigated responses is presented in table 1.

Table 1: Process parameters and response values of central composite design

| Code | Polymer ratio (Eudragit E100 : EC) | Concentration of PVA (% w/v) | Particle Size (µm) | Entrapment efficiency (%) | Buoyancy (%) | Cumulative drug release (%) |
|------|-----------------------------------|------------------------------|-------------------|--------------------------|-------------|-----------------------------|
| F1   | 0 (1:4)                           | 0 (0.75)                     | 336.1             | 72.2                     | 52.52       | 87.11                       |
| F2   | -1.414 (1:1.68)                   | 0 (0.75)                     | 305               | 83.67                    | 53.31       | 94.43                       |
| F3   | 0 (1:4)                           | 0 (0.75)                     | 352.2             | 74.79                    | 52.66       | 84.81                       |
| F4   | 0 (1:4)                           | 0 (0.75)                     | 383.2             | 76.35                    | 56.05       | 86.15                       |
| F5   | 1 (1:6)                           | -1 (0.5)                     | 502.4             | 89.83                    | 78.59       | 77.78                       |
| F6   | 1 (1:6)                           | 1 (1.0)                      | 424.3             | 81.36                    | 56.97       | 82.33                       |
| F7   | 1 (1:6)                           | 1 (0.75)                     | 374.2             | 75.12                    | 54.25       | 87.59                       |
| F8   | 1 (1:6)                           | -1 (1.0)                     | 332.2             | 79.05                    | 45.43       | 92.5                        |
| F9   | 1 (1:6)                           | 1.414 (1.1)                  | 295.7             | 80.89                    | 50.85       | 90.45                       |
| F10  | 1 (1:6)                           | -1 (0.5)                     | 432.1             | 84.11                    | 60.77       | 87.72                       |
| F11  | 1.414 (1:8.68)                    | 0 (0.75)                     | 447               | 86.46                    | 69.58       | 74.26                       |
| F12  | 0 (1:4)                           | 0 (0.75)                     | 395.2             | 75.87                    | 57.31       | 84.48                       |
| F13  | 0 (1:4)                           | -1.414 (0.4)                 | 482.6             | 93.74                    | 72.58       | 79.15                       |

Characterization of floating microspheres

Physico-chemical analysis

Fourier Transform Infra-Red spectroscopy analysis (FTIR) and thermal analysis were done to determine any possible chemical interaction between drug and excipients. For FTIR analysis, the samples were finely powdered and mixed with Kbr and scanned using an FTIR spectrophotometer (IR Affinity, Shimadzu) in the wavelength region between 4000 and 400 cm⁻¹.

The thermal analysis of samples was done by Differential Scanning Calorimetry (DSC) by Differential Scanning Calorimeter (DSC 25, TA instruments). Samples of 2.5–5 mg were placed into an aluminum pan and heated at a constant rate (10 °C min⁻¹) from 30 to 300 °C under nitrogen atmosphere.

Powder X-ray diffraction analysis was done to monitor the nature of the pure drug and after encapsulation into microspheres by X-ray diffractometer (Rigaku Miniflex-II X-ray diffractometer). The data set was collected in continuous scan at step size 0.04 ° 20 and angle range of 10°–70°.

Particle size and particle surface morphology

Particle Size analysis was done using the mastersizer (Microtrac S-3500, USA) equipped with a liquid handling system while the morphology of particles was observed by SEM.

Drug content

For determining the proportion of the drug that got entrapped in microspheres, 10 mg of microspheres containing drug was dissolved in methanol. The samples were filtered through a 0.45 µm membrane and after appropriate dilution, the samples were assayed using UV-visible spectrophotometer (Cary 5000, Varian, Australia) at 262 nm against blank methanol containing the same quantity of blank microspheres. The drug content of floating microspheres can be calculated by dividing the weight of the drug in microspheres by weight of microspheres [25].

Drug entrapment efficiency

The drug entrapment efficiency in floating microspheres can be estimated by dissolving a predetermined amount of microspheres in methanol, filter the samples and analyze spectrophotometrically after appropriate dilution if required [25, 26].

\[ \% \text{Entrapment Efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100 \]

In vitro floating ability

This study is carried out by using USP Type I dissolution apparatus stirred at 100 rpm at 37±0.5 °C. Weight amount of floating microspheres were spread on the surface of simulated gastric fluid (pH 1.2) containing surfactant. After a specified period, both the floating and settled fraction of microspheres were collected separately, dried and weighed [27]. The floating ability or percent buoyancy was calculated by the given formula

\[ \% \text{Buoyancy} = \frac{\text{Weight of hollow microspheres}}{\text{Total weight of hollow and settled microsphere}} \times 100 \]

In vitro drug release study

The drug release rate from microspheres was carried out using USP dissolution apparatus II. Microspheres equivalent to 30 mg of the drug were treated with 900 ml simulated gastric fluid (pH 1.2) containing 0.5% w/v tween 80 having a paddle rotation speed of 100 rpm at 37±0.5 °C. The samples were withdrawn at regular time intervals and replaced it with fresh medium to maintain the sink conditions, then the samples were passed through a 0.45 µm membrane filter, and analyzed spectrophotometrically at 258 nm. All experiments were carried out in triplicate.

Drug release kinetics

The mechanism of drug release from microspheres were determined by applying different kinetic models to the data obtained from in vitro analysis such as Zero-order kinetics (percent release vs. time), first-order kinetics (log percent release vs. time), Higuchi’s model.
(percent release vs. square root of time), Korsemeyer and Peppa’s model (log cumulative percentage drug release vs. log time) [28,29].

Stability studies

The optimized formulation was tested for stability profile at normal and accelerated conditions as per ICH guidelines [30]. The formulation was placed separately in borosilicate screw-capped glass container and stored at normal room temperature (25±2 °C), freezing temperature (5±3 °C) and under accelerated conditions (40±2 °C/75±5% RH) for 6 mo. After predetermined time intervals, the samples were evaluated for visual physical appearance, Drug content, buoyancy and drug release studies [31, 32].

RESULTS AND DISCUSSION

Effect of process conditions

Solvent evaporation technique is affected by a large number of process variables. In the present study, the effect of process variables such as stirring rate, system temperature and stirring time was observed over percent yield and physical appearance of floating microspheres. For that 400 mg of ethyl cellulose was used as low-density polymer and 100 mg of Eudragit E100 polymer was used as release modifier of polymer and 0.75 %w/v of PVA used to prepare blank microspheres. The effect of the above process variables is given in table 2.

At low stirring speed, the harder globules of the polymer formed due to coalescence and aggregation while at higher speed the microspheres breakdown to form irregular particles. At 40 °C temperature, the solvent diffuses into aqueous phase at an intermittent rate and provide sufficient time for droplet formation and hardening of hollow microspheres. The longer the stirring time will provide enough time for the solvent to diffuse and thus improve the yield. For this investigation we found that optimized conditions for preparation of hollow microspheres were stirring rate of 350 rpm, stirring time of 2 h and system temperature 40 °C.

Table 2: Effect of process variables

| Process conditions     | % Yield | Physical appearance       |
|-----------------------|---------|---------------------------|
| Stirring Rate (rpm)   |         |                           |
| 150                   | 52.25   | Large particles           |
| 350                   | 57.00   | Spherical particles       |
| 900                   | 54.76   | Irregular shape           |
| System Temperature    |         |                           |
| Room temperature      |         |                           |
| 40 °C                 | 57.26   | Spherical particles       |
| 60 °C                 | 56.04   | Irregularly shaped particles |
| Stirring Time         |         |                           |
| 30 min.               | -       | Sticky Lumps              |
| 1 h                   | 53.79   | Slightly sticky particles |
| 2 h                   | 58.04   | Spherical particles       |

Physico-chemical analysis

The change in frequency and bandwidth of different interacting groups in the spectrum of the mixture of drug and excipients are studied by FTIR analysis [33]. The FT-IR spectral bands of itraconazole, ethylcellulose, Eudragit E100, placebo microspheres and optimized drug loaded formulation are shown in fig. 1. On the interpretation of spectra, it is clear that all characteristic peaks of the drug are intact. Hence, no major shift or addition of new peaks indicated that no significant chemical interaction between drug and polymers.

DSC and XRD analysis were carried out to study the change in the physical state of drug and/or any significant drug and excipients interactions [34]. Fig. 2 shows DSC thermograms of itraconazole, ethyl cellulose, Eudragit E100, physical mixture and optimized batch. The DSC thermogram of itraconazole shows a sharp endothermic peak at 167.8 °C. Thermograms of ethyl cellulose and Eudragit E100 showed a broad endothermic peak at 56.77 °C and 65.36 °C respectively, which represent the melting of polymers. The endothermic peak of itraconazole appears in drug-excipients physical mixture with a slight change in temperature which indicates the crystalline nature of the drug and the absence of any chemical interaction at solid-state. The DSC results of an optimized batch of microspheres showed a small blunt endothermic peak of itraconazole was observed at 161.32 °C, due to a reduction in the crystallinity of drug by its solubilization in the polymer matrix.
The X-ray diffraction pattern shown in Fig. 3, the pure drug showed a range of sharp and distinctive peaks at 2θ angle of 23.58 °, 20.46 °, 17.58 ° and 14.58 °, having maximum peak intensity at 2θ angle of 20.46 ° indicating crystalline nature of the drug. The physical mixture showed peaks of itraconazole. The DSC results were confirmed by diffractograms of the optimized batch which exemplify the absence of sharp distinctive peaks of itraconazole.

Optimization of data analysis
In the present study, the central composite experimental design was employed as it adequately described the interaction between the factors with the least number of experimental trial runs. The summary of the experimental data and observed responses were given in Table 1.

All Observed responses were fitted to various polynomial models. It was seen that the particle size (R₁) and percent cumulative drug release (R₄) fitted best into linear response surface model ($p$-value 0.0004 for $R₁$, $p$-value<0.0001 for $R₄$) while the entrapment efficiency (R₂) and percentage buoyancy (R₃) was found to be fitted best into quadratic response surface model ($p$-value 0.0004 for $R₂$, $p$-value 0.0002 for $R₃$) with no transformations of data. The polynomial equations generated for responses in terms of coded values given below:

$$R₁ (\mu m) = 389.4 + 45.4023 X₁ + 5.52896 X₂$$

$$R₂ (%) = 74.8666 + 1.49696 X₁ + 3.96283 X₂ + 0.8525 X₁ X₂ + 4.44887 X₁^2 + 5.57387 X₂^2$$

$$R₃ (%) = 54.558 + 7.79616 X₁ + 7.21136 X₂ + 0.93 X₁ X₂ + 3.7835 X₁^2 + 3.9185 X₂^2$$

$$R₄ (%) = 85.2892 + 6.07934 X₁ + 3.16383 X₂$$

The polynomial equations demonstrate the relationship between the process variables and response variables. A model was considered to be significant if the $P$-value<0.05. The synergistic effect and antagonistic effect can be illustrated from the positive and negative signs respectively. The sign and magnitude of factor value have a relative impact on the responses. Table 3 showed the result of ANOVA analysis on models indicate that the $F$-value of response surface model for all responses is significant ($P<0.05$) with non-significant ‘lack of fit’ ($P>0.05$) which ensure the reliability of the applied model. The predicted $R^2$ and adjusted $R^2$ were in good agreement which signifies the reliability of models. In addition to the above, adequate precision measure signal to noise ratio, higher values of adequate precision (>4) indicate that developed models are fit to navigate the design space.
From the polynomial equations, the contour plots and 3D response surface graphs were generated (displayed in fig. 4) signifies that the polymer ratio and concentration of PVA carry a significant effect on particle size, entrapment efficiency, buoyancy, and drug release.

Fig. 4 (a) showed a decrease in particle size in an almost linear manner with an increase in the concentration of PVA as it reduces the interfacial tension between the particles and stabilizes the polymer droplets in the aqueous phase which result in coalescence of particles. The increase in the concentration of ethylcellulose in the ratio of polymers, the particle size increases in linearly. The maximum particle size observed at a high ratio of ethylcellulose and a lower concentration of PVA.

Fig. 4 (b) depicted that the drug entrapment efficiency significantly increased with increase in the ratio of ethylcellulose concentration while Eudragit E100 tends to decrease the entrapment of drug as it increases the permeability of microspheres which leads to diffusion of drug towards external phase [20]. On the other hand, the concentration of PVA has a pronounced effect on entrapment efficiency, as it decreases with increase in the concentration of PVA. However, the influence of the concentration of PVA is more significant than that of the ratio of polymers.
The effect of process variables on buoyancy is shown in fig. 4(c). The buoyancy signifies the floating ability of microspheres owing to their hollow structure. The density of polymers and the size of particles play an important role in buoyancy [35]. As the size of the particle increases the density decreases which directly increase the floating ability of microspheres. Hence, increase in buoyancy can be directly related to increase in polymer ratio especially with the increase in the concentration of ethylcellulose, a low-density hydrophobic polymer but inversely related to increasing in the concentration of PVA as increased concentration of surfactant decrease the particle size which directly decreases the buoyancy. Similarly, the buoyancy of microspheres also decreases up to some extent with the increase in Eudragit E100 polymer due to dissolution and ingestion of simulated gastric fluid into microspheres [19].

The response surface plot of percent cumulative drug release shown in fig. 4(d). The finding from in vitro drug release study states the biphasic release pattern of formulations with initial burst release due to surface-associated drug particles followed by slow diffusion of the drug from the polymer matrix, as displayed in fig. 5. It was observed that the drug release increases with the increase in the concentration of Eudragit E100, because of soluble nature of Eudragit E100 polymer in simulated gastric fluid. Concerning the effect of emulsifier, PVA resulted in a significant increase in the release rate. This can be explained by the relative increase in surface area by the reduction in particle size and it also increases the wet ability of particles which subsequently results in increased drug release [36].

Floating microspheres were subjected to numerical optimization tool along with desirability approach of Design-Expert software (Version 11.0.0, Stat-Ease Inc., Minneapolis, MN). The goal is to obtain the optimum values of the independent variables. Optimization was performed and the optimal calculated parameters adjudged were having the ratio of polymers \(X_1\) 2:1 and concentration of PVA \(X_2\) 0.5 %w/v with the highest desirability. The results experimental and predicted responses for final optimized concentration are tabulated in table 4.

**Table 4: Comparison of experimental results with predicted values of optimized formulation**

| \(X_1/X_2\) | Response | Experimental | Predicted | %Error |
|-------------|----------|--------------|-----------|--------|
| 2:1/0.5     | \(R_1\)  | 432.1        | 399.28    | 8.21   |
|             | \(R_2\)  | 84.11        | 86.50     | -2.76  |
|             | \(R_3\)  | 60.77        | 62.60     | -2.92  |
|             | \(R_4\)  | 87.72        | 88.20     | -0.54  |

**SEM analysis**

SEM observed the shape and morphology of microspheres as shown in fig. 6. The analysis confirmed the smooth and spherical shape of particles. The microsphere shell also showed some small pore over it and having an internal hollow cavity. The pore over the surface may be due to the diffusion of solvent and the central hollow cavity formed by the generation of gaseous phase inside the polymer droplet by the evaporation of entrapped solvent inside the microspheres.

**Fig. 6: SEM image of the surface view of a hollow microsphere; (b) SEM image showing central hollow cavity**
Drug release kinetics

In order to determine the mechanism of drug release profile of optimized batch, the in vitro release data was subjected to various mathematical kinetic models and regression coefficient value after interpretation of data comes out to be 0.936 for zero-order, 0.990 for first order, 0.989 for Higuchi’s model and 0.994 for Korsmeyer and Peppa’s model and drug release exponent (n) comes out to be 0.531. The mechanism of drug release was found to be diffusion and erosion controlled as the regression coefficient value is maximum for Korsmeyer and Peppa’s model [29].

Stability studies

All the parameters studied for the stability of optimized formulation were found to be satisfying at the end of six months (table 5). The formulation showed no significant change in properties over time at different temperature and humidity conditions. The microspheres remained well within the acceptance criteria during the proposed study at accelerated conditions. Hence, floating microspheres are chemically and physically stable and retain their pharmaceutical properties for over 6 mo.

Table 5: Stability study profile

| Parameters                          | 0 mo       | 1 mo       | 2 mo       | 3 mo       | 6 mo       |
|-------------------------------------|------------|------------|------------|------------|------------|
| Refrigerator conditions             |            |            |            |            |            |
| Visual Appearance                    | White      | No physical change | No physical change | No physical change | No physical change |
| Drug Content                        | 17.72±0.30 | 17.70±0.12 | 17.68±0.15 | 17.67±0.20 | 17.33±0.25 |
| Buoyancy                            | 60.77±1.02 | 60.73±0.75 | 60.65±0.80 | 60.5±1.05  | 60.00±1.25 |
| In vitro drug release               | 87.72±1.23 | 87.64±0.78 | 87.57±0.90 | 87.4±1.24  | 87.25±1.40 |
| Room temperature (25±2°C)           |            |            |            |            |            |
| Visual Appearance                    | White      | No physical change | No physical change | No physical change | No physical change |
| Drug Content                        | 17.72±0.30 | 17.61±0.23 | 17.48±0.49 | 17.24±0.41 | 16.70±0.52 |
| Buoyancy                            | 60.77±1.02 | 60.65±0.95 | 60.40±1.12 | 60.15±1.24 | 59.80±1.06 |
| In vitro drug release               | 87.72±1.23 | 87.50±0.87 | 87.25±0.76 | 86.75±1.12 | 86.22±1.52 |
| Accelerated conditions (40±2°C,75±5% RH) |            |            |            |            |            |
| Visual Appearance                    | White      | No physical change | No physical change | No physical change | Small aggregates formed |
| Drug Content                        | 17.72±0.30 | 17.35±0.28 | 17.12±0.54 | 16.85±0.38 | 16.00±0.44 |
| Buoyancy                            | 60.77±1.02 | 60.50±0.50 | 60.15±1.08 | 59.95±0.95 | 59.50±1.24 |
| In vitro drug release               | 87.72±1.23 | 87.53±1.12 | 87.15±0.70 | 86.54±0.35 | 85.45±1.44 |

All values are the mean±SD (n=3)

CONCLUSION

Itraconazole-loaded non-effervescent floating hollow microspheres were successfully prepared by emulsion–solvent diffusion evaporation technique employing optimal process conditions. The central composite design of response surface methodology approach is a very useful statistical technique to conclude the effect of independent variables on the responses. The prepared microspheres characterize by particle size, percent entrapment efficiency, in vitro floating ability and in vitro drug release, and were observed that the formulations were significantly affected by the ratio of low-density polymer and release modifier and concentration of PVA. The result of the stability study depicted that the floating microspheres were found to be stable for 6 mo. The presence of PVA as an emulsifier and pH-dependent Erudgat E 100 as a release modifying polymer facilitate significant drug release in simulated gastric fluid, the desired medium for drug absorption. Besides, the drug release kinetics follows Korsmeyer Peppas model as the drug release occurs by diffusion and erosion controlled mechanism. The hollow microspheres with a release modifying polymer is a useful approach to retain the formulation at its absorption site and facilitate the drug release.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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