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Design and Characterization of Gastroretentive Microspheres of Irbesartan

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Abstract: The objective of the current study was to develop a Floating drug delivery system for Irbesartan, a model drug. The study involved assessing various processing parameters, such as buoyancy studies and in vitro drug release studies. Independent variables included Drug: polymer ratio (X1), Ethyl Cellulose (Ethocel) 18-22 cps, and Eudragit S-100 polymers ratio (X2). Dependent variables were Y1 % Practical Yield, Y2 % Buoyancy, and Y3 % Drug entrapment efficiency (EE). To prepare the floating microspheres containing Irbesartan, a modified Emulsion solvent evaporation technique was employed. Different formulations were prepared using drug to polymer ratios of 1:1, 1:2, and 1:3. The proportions of the polymers had a significant impact on the drug release. All formulations demonstrated diffusion dominant drug release and were deemed stable.

Keywords: Irbesartan, Solvent evaporation, Ionic gelation, Floating microspheres, Gastro retentive drug delivery system

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Introduction

Because of its convenience of administration, cost effective therapy, patient compliance, and flexibility of formulation, oral drug delivery is by far the most used modality of drug delivery. The stomach emptying time has some restrictions in oral sustained drug delivery formulations. Due to unpredictable and too speedy gastrointestinal transit, incomplete drug release from the dosage form into the absorption window could result in diminished efficacy of the provided dose. According to recent studies and patent filings, there is an increasing interest in innovative dosage forms that stay in the stomach for a lengthy and predictable period (Dixit, 2011).

The ability to extend and manage the time it takes for the stomach to empty is crucial for dosage forms that need to stay in the stomach for longer periods of time compared to conventional dosage forms. Developing controlled release systems to improve absorption and bioavailability is challenging, particularly when it comes to keeping the dosage form in the desired area of the gastrointestinal system. The absorption of drugs from the gastrointestinal tract is a complex process that is influenced by various factors. According to conventional wisdom, the amount of drug absorbed in the gastrointestinal system is directly related to the amount of time the drug remains in contact with the mucosa of the small intestine. For drugs that are only partially absorbed, the small intestinal transit time is an important factor (Chandel *et al*., 2012).

Gastroretentive systems have the ability to remain in the stomach for several hours, significantly prolonging the time that drugs stay in this region. This prolonged stomach retention enhances bioavailability, reduces drug wastage, and improves solubility for drugs that are only partially soluble at high pH levels. Additionally, gastroretentive systems can transport drugs to both the stomach and the proximal small intestine. The ability to retain drugs in the stomach makes it easier to develop new medications with innovative therapeutic options and significant benefits for patients (Mayavanshi and Gajjar, 2008).

Controlling the placement of a drug delivery system in a specific area of the gastrointestinal tract, such as gastroretention, offers several advantages for targeted drug delivery in the stomach region. These benefits include (Garg and Gupta, 2008; Nayak *et al*., 2010):

(i) The longer the stomach residence time, the better the drug absorption

(ii) Enhancement of bioavailability

(iii) The dosing frequency is being reduced.

(iv) Minimizing adverse effects in other parts of the body.

(v) Overall, cutting in the health care cost.

Gastro retentive drug delivery system (GRDDS) has been advantageous especially for drugs:

(i) Drugs that have a local effect on the stomach.

(ii) Which has a stomach absorption window.

(iii) Drugs that are unstable in the intestine or colon.

(iv) Drugs having poor solubility at high pH values (Singh and Rathore, 2012).

In this research, we have examined Irbesartan, a white, amorphous powder that belongs to the class of non-peptide AIIRAs. Irbesartan specifically binds to AT1 receptors, thereby limiting the physiological effects of angiotensin II. The Renin-Angiotensin system plays a crucial role in regulating blood pressure, fluid balance, and electrolyte balance. Renin, an enzyme produced by the kidneys, converts the inactive plasma protein angiotensinogen into angiotensin I (Ang I). Ang I is then converted to angiotensin II (Ang II) by the angiotensin-converting enzyme (ACE). Ang II binds to AT1 receptors in the plasma, leading to increased cardiac contractility, salt reabsorption, and vasoconstriction, ultimately resulting in elevated blood pressure. ARBs (Angiotensin Receptor Blockers) work by blocking AT1 receptors, thereby reducing blood pressure. Several studies have supported the efficacy of ARBs in lowering blood pressure (Kouchak and Bardrian, 2007; Chambers *et al*., 2008; Burnier, 2009).

The objective of this study was to formulate and evaluate the regiospecific floating microspheres of antihypertensive drug and study the effect of different polymers and different concentration of individual polymers on the floating behavior of microspheres to enhance patient compliance and minimize dosing frequency.

Materials and Methods

Reagents and Chemicals:

Factorial Design:

The state-of-the-art computerized optimization software Design Expert was utilized to generate the experimental design. In this particular research study, the independent variables chosen were the Drug: polymer ratio (X1) and the ratio of Ethyl Cellulose (Ethocel)18-22 cps to Eudragit S-100 polymers (X2). The dependent variables, on the other hand, were Y1 % Practical Yield, Y2 % Buoyancy, and Y3 % Drug entrapment efficiency (EE).

Fabrication of Floating Microspheres of Irbesartan:

A modified emulsion solvent evaporation technique was utilized to prepare floating microspheres containing Irbesartan. Different formulations were prepared using drug to polymer ratios of 1:1, 1:2, and 1:3. The polymer content consisted of a mixture of Eudragit S100 and Ethyl Cellulose 22cps in varying concentrations. The drug, polymers, and βCD were dissolved in a mixture of Methanol and Dichloromethane (1:2 w/v). The solution was then administered from the bottom side into a 0.4% w/v Poly vinyl alcohol solution (400mL) using a 22-gauge needle. Stirring was conducted at 40°C for 1 hour at 300 rpm using a propeller-type agitator and magnetic stirrer. The resulting floating microspheres were filtered using Mann filter paper, washed with water, and dried at 40°C overnight. To prevent the solidification and aggregation of the polymer on the surface, a new method of introducing the polymer solution from the bottom side was adopted, as established by Gupta *et al*. (2014). β-cyclodextrin was added to enhance the solubility and dissolution of Irbesartan. An optimization study was conducted using a 32 factorial design.

Characterization of Irbesartan Floating Microsphere:

The micromeritics characteristic of the microsphere demonstrates that the acquired measurements were comfortably within the prescribed range for powder to possess desirable flow characteristics. This outcome unequivocally indicates that the fabricated hollow microspheres exhibit commendable flow properties.

Particle Size Determination:

The optical microscopy method was utilized to determine the particle size, which plays a crucial role in the floating ability and drug release from microspheres. The mean particle size of the hollow microspheres ranged from 458.06±5.4 to 471.90±1.2 µm, as indicated in Table 2.When the size of the microspheres is smaller, the drug release rate increases due to the larger surface area, while the floating ability decreases. Conversely, larger microspheres enhance the floating ability and result in a sustained release rate. It was observed that the concentrations of Ethyl cellulose and Eudragit S 100 have an impact on the particle size. With an increase in Ethyl cellulose concentration, the particle size also increases due to the higher viscosity at higher levels. Consequently, higher concentrations of Ethyl cellulose lead to lower stirring efficiency. This nature of the polymer causes rapid precipitation and hardening, preventing further reduction in particle size during solvent evaporation. On the other hand, an increase in Eudragit S 100 concentration leads to a decrease in particle size.

DCM is the preferred solvent for the preparation of floating microspheres as it aids in the formation of a hollow inner core. However, the high amount of DCM in the developed floating microspheres of Irbesartan resulted in an increase in the average size of the microspheres.

Determination of % Practical Yield:

The impact of the drug polymer ratio on the practical yield percentage of the resulting microspheres was investigated. The practical yield percentage of various formulations was determined by weighing the dried Irbesartan microspheres. The yield of the product was influenced by the clumping and adherence of the

polymer to the stirrer blades and beaker wall during microsphere formation. The practical yield percentage of different formulations ranged from 75.96±2.7 to 87.56±2.4%, as indicated in Table 3.

A polynomial equation was derived to establish the mathematical relationship for the measured response (%Practical Yield). The equation is as follows:

%Practical Yield = +77.49 + 2.73 * A - 2.05 * B - 1.17 * AB - 0.51 * A^2 + 3.99 * B^2.

The successful production of microspheres was heavily influenced by the concentration of the polymer in the mixed solvent. It was observed that increasing the polymer concentration resulted in larger microspheres and a higher practical yield.

To develop the formulations of Irbesartan loaded floating microspheres, a modified solvent evaporation method was employed. In this method, the drug-polymeric oral solution was added to a stirring solution of PVA with a concentration of 0.4% w/v from the bottom side. This technique was used to prevent polymer aggregation on the top of the PVA, resulting in the production of more spherical microspheres and a satisfactory yield of the product. The percentage yield of floating microspheres varied depending on the polymer concentration. The practical yield of the developed microspheres was found to increase as the concentration of Ethyl cellulose increased. These findings align with previously reported results of Irbesartan microsphere preparation by Khan *et al*. (2022). On the other hand, a decrease in the practical yield was observed with an increase in the concentration of Eudragit S 100. The response surface and contour plots shown in Figures 5 and 6 indicated that both the drug polymer ratio and the ratio of EC to Eudragit had an impact on the practical yield of the developed floating microsphere of Irbesartan. Overall, the studies conducted by Tatane (2011) and Behera *et al.* (2012) revealed that an increase in the drug polymer ratio led to an increase in the practical yield.

In-vitro Buoyancy Test:

In order to evaluate the floating characteristics, the microspheres were dispersed in a solution of 0.1N HCl containing 0.02% Tween 80. This was done to mimic the wetting effect of gastric fluid during movement. The addition of Tween 80 served to counteract the downward force exerted on the liquid surface by reducing the surface tension of the medium in 0.1N HCl. The ability of the microspheres to float was primarily influenced by their density. Furthermore, the internal structure of the microspheres played a significant role in determining their floating property. It was observed that the floating ability of different formulations varied depending on the ratio of Eudragit to Ethyl cellulose. The percentage of buoyancy for the different formulations ranged from 72.78±5.8% to 82.22±6.2%, as indicated in Table 4.

% Drug Entrapment Efficiency (*EE*):

The drug entrapment efficacies of different formulations were in range of 67.98±1.23 to 87.45±3.2% w/w as shown in following Table 5. of all batches of microspheres. The drug concentration and solvent volume were kept constant in all batches of microspheres. The particle sizes of floating microspheres were determined to be in the range of 65 to 90 µm when using the solvent evaporation technique, and 450 to 600 µm when using the ionic gelation technique (Table 6).

Drug loading Efficiency:

The drug loading efficiencies of the microspheres varied between 14.69±1.41 to 23.26±0.11 % w/w, as indicated in Table 6. It was noted that an increase in the drug: polymer ratio resulted in a decrease in the drug loading of the Irbesartan floating microspheres that were developed.

In-vitro Drug Release Study:

The primary objective of developing floating microspheres is to prolong their retention in the stomach, thereby extending the duration of drug

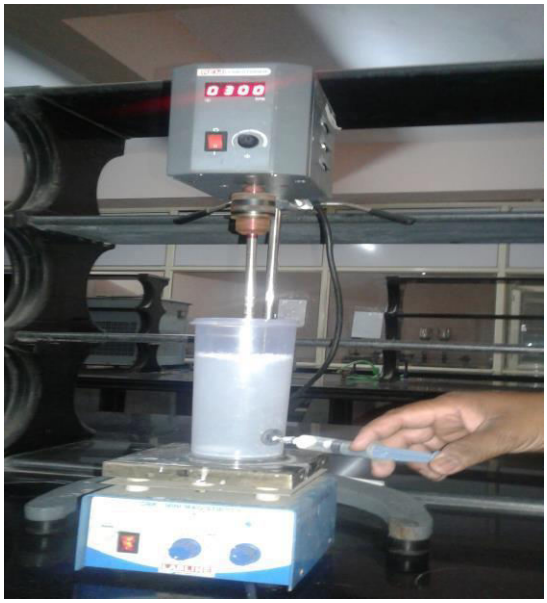


Fig. 1: Photograph showing technique used for fabrication of floating Microsphere.

Table 1: Micrometrics properties of floating Microspheres

Batch No.	Angle 0f Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Index (%)
F1	33.42±1.22	0.140±00.02	0.162±0.044	1.15±0.01	13.5±0.04
F2	34.99±2.90	0.152±0.07	0.180±0.31	1.18±0.12	15.55±0.12
F3	34.99±1.32	0.145±0.14	0.169±0.14	1.16±0.04	14.2±0.45
F4	33.69±1.89	0.130±0.23	0.153±0.21	1.18±0.08	15.03±0.09
F5	36.38±1.76	0.142±0.41	0.168±0.15	1.18±0.14	15.47±0.08
F6	36.43±1.54	0.148±0.05	0.176±0.44	1.19±0.32	15.9±0.15
F7	38.65±1.34	0.151±0.09	0.175±2.34	1.15±0.14	13.7±0.16
F8	34.21±1.67	0.137±0.11	0.158±0.08	1.15±0.006	13.2±0.04
F9	34.21±1.85	0.129±0.13	0.147±0.04	1.13±0.05	12.2±0.05

Table 2: Particle Size of Irbesartan Floating Microsphere Batches

Batch	Size (µm)
F1	465.24±2.3
F2	471.90±1.2
F3	478.67±7.9
F4	463.88±5.9
F5	464.74±6.4
F6	471.32±4.4
F7	468.90±8.7
F8	466.21±5.8
F9	458.06±5.4

release. In order to assess the drug release, an *in vitro* experiment was conducted using a paddle type dissolution apparatus. The results, as depicted in Figure 8, demonstrate the drug release from the floating microspheres. The cumulative drug release percentages for formulations F1, F2, F3, and F4 were found to be 99.28±2.11% at 10 hours, 92.52±1.10% at 12 hours, 78.35±0.65% at 12 hours, and 99.39±2.48% at 9 hours, respectively. On the other hand, formulation F5 exhibited a consistent drug release of 93.22±0.9% at 10 hours. Formulations F6, F7, F8, and F9 displayed cumulative drug release percentages of 84.89±0.55%, 97.31±0.24% at 8 hours, 95.79±2.71% at 12 hours, and 87.07.00±0.62% at 12 hours, respectively. Notably, formulation F8 demonstrated the optimal drug release of 95.79±2.71% over a period of 12 hours. The addition of βeta Cyclo Dextrin as a complexing agent enhanced the solubility of the drug in the gastrointestinal fluid prior to absorption. Consequently, the solubility and dissolution of Irbesartan were significantly increased through βCD complexation.

Optimization Data Analysis for the Floating Microsphere Dosage Form:

Design Expert software was used to fit responses observed for nine formulations. The software displayed the values of R2, SD, and % coefficient of variance for all the formulations. In order to determine the most appropriate model, the selected responses for statistical optimization were fitted to linear, interactive, and quadratic models. The linear model was applied to DEE%, Buoyancy, and other responses, while the quadratic model was used for the Practical yield % response. The results of ANOVA indicated that the model was significant for all three response variables.

Selection of Optimized Batch:

The optimized formulation batch should demonstrate the highest drug release at 12 hours, excellent vitro buoyancy, and efficient drug entrapment. The findings from the experimental design formulations and kinetic modeling of the drug release study indicated that formulation F8 meets all the desired requirements. Therefore, it was chosen as the optimized formulation and will be considered for further *in vivo* study. Mathematical relationship in the form of polynomial equation for the measured response (% EE) was obtained and given in equation below:

$$\%EE=+78.08+2.46* A+7.35* B$$

Table 3: Practical yield of Irbesartan floating Microsphere batches F1-F9

Batch	%Practical Yield
F1	78.64±3.05
F2	83.36±4.4
F3	87.56. ±2.4
F4	76.14±2.9
F5	77.19±2.03
F6	79.34±3.6
F7	75.96±2.7
F8	81.11±4.2
F9	80.21±2.4

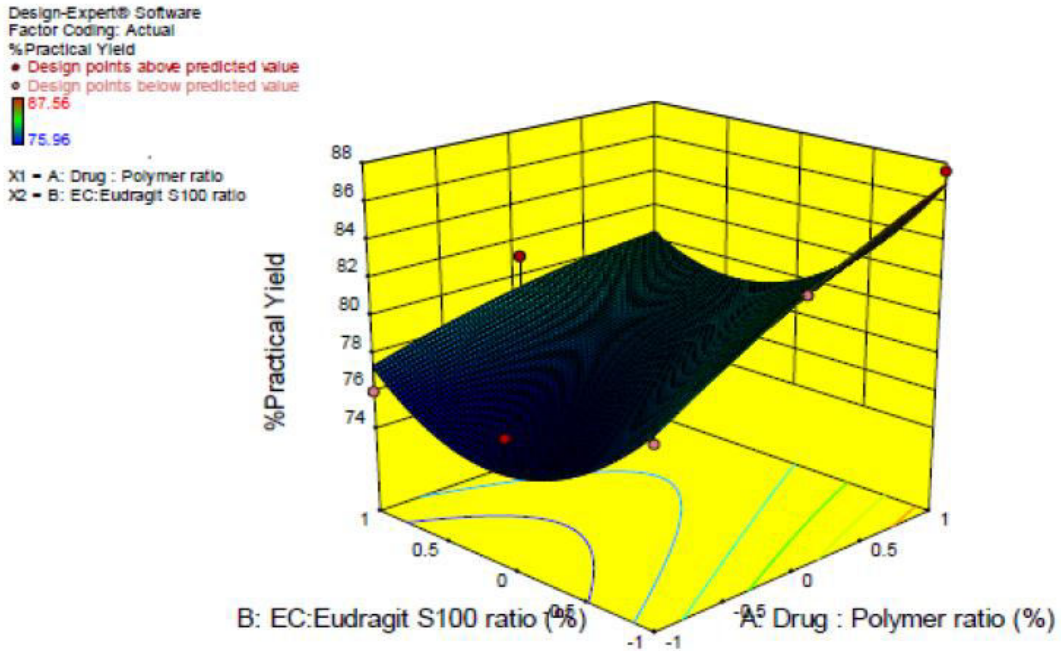


Fig. 2: A response surface plot is utilized to illustrate the impact of the Drug: polymer ratio (X1) and the ratio of Ethyl Cellulose 18-22 cps to Eudragit S-100 polymers (X2) on the practical yield percentage.

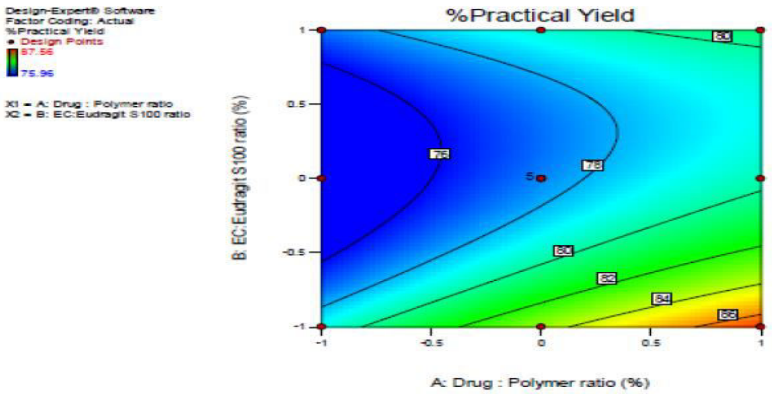


Fig. 3: Contour plots presenting the effects of Drug: polymer ratio (X1), Ethyl Cellulose 18-22 cps and Eudragit S-100 polymers ratio (X2) on % practical yield.

Table 4: Buoyancy of Irbesartan floating Microsphere Batches F1-F9

Batches	% Buoyancy after 12 h
F1	77.88±2.2
F2	79.51±1.3
F3	82.22±6.2
F4	75.55±7.2
F5	76.88±6.3
F6	77.65±5.1
F7	72.78±5.8
F8	73.98±7.8
F9	76.38±4.4

Table 5: DEE of Irbesartan floating Microsphere Batches F1-F9

Batch	% DEE
F1	67.98±1.23
F2	69.40±2.22
F3	72.15±3.15
F4	74.77±0.8
F5	78.88±0.6
F6	82.68±1.2
F7	84.78±3.2
F8	86.45±2.6
F9	87.45±3.2

Table 6: DLE of Irbesartan floating Microsphere Batches F1-F9

Batch	%DEE
F1	67.98±1.23
F2	69.40±2.22
F3	72.15±3.15
F4	74.77±0.8
F5	78.88±0.6
F6	82.68±1.2
F7	84.78±3.2
F8	86.45±2.6
F9	87.45±3.2

Table 7: Summary of results of regression analysis for responses and analysis of Variance for Y1 % Practical Yield, Y2 %Buoyancy, Y3 % Drug entrapment efficiency, of optimized formulation F8

Parameters	DF	SS	MS	*F*	*p* - Value	R^2	SD	CV %
% **Practical Yield**								
Model	5	122.44	24.49	17.7	0.0008	0.9267	1.18	1.49
Residual	7	9.68	1.38	-	-	-	-	-
Total	12	132.12	25.87	-	-	-	-	-
% **Buoyancy**								
Model	2	62.01	31.01	141.6	< 0.0001	0.9659	0.47	0.61
Residual	10	2.19	0.22	-	-	-	-	-
Total	12	64.2	31.23	-	-	-	-	-
% **EE**								
Model	2	360.84	180.4	58.38	< 0.0001	0.9211	78.1	2.25
Residual	10	30.91	3.09	-	-	-	-	-
Total	12	391.74	183.5	-	-	-	-	-

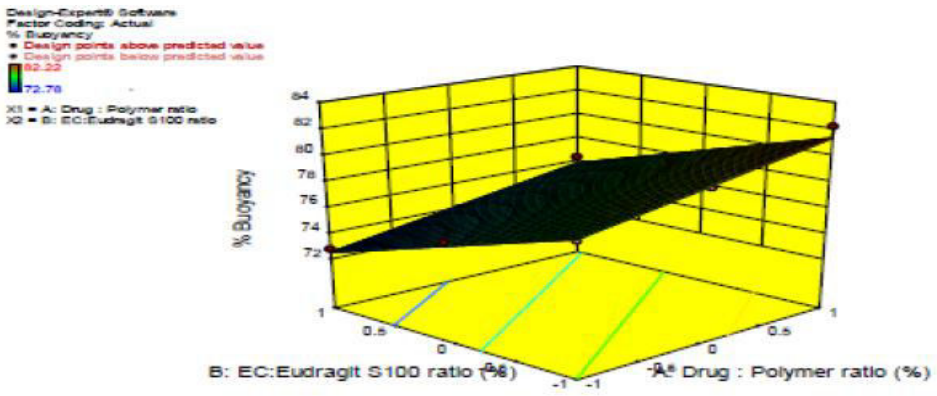


Fig. 4: Response surface plots presenting the effects of Drug: polymer ratio (X1), Ethyl Cellulose 18-22 cps and Eudragit S-100 polymers ratio (X2) on % EE.

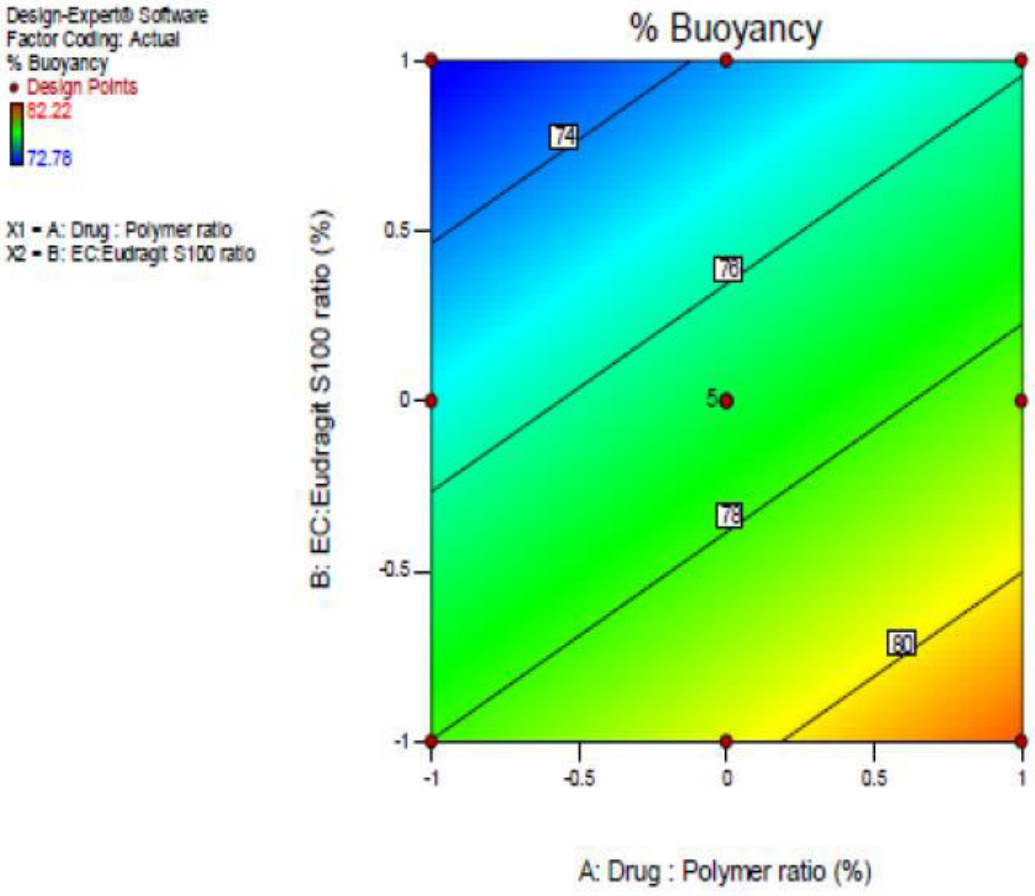


Fig. 5: Contour plots presenting the effects of Drug: polymer ratio (X1), Ethyl Cellulose 18-22 cps & Eudragit S-100 polymers ratio (X2) on % EE.

From Table 6 it was observed that as the amount of Eudragit S 100 increases increase in the drug entrapment efficiency occurs. Also decrease in the Drug entrapment efficiency is observed as the amount of Ethyl cellulose increased[100]. From response surface & contour plots shown in Figures 6 and 7 it was found that entrapment efficiency is not significantly affected by Drug: Polymer ratio but affected by the Ethyl cellulose: Eudragit S 100 ratio and from above equation concluded that Eudragit S 100 is more efficient polymer for encapsulating the drug in this developed floating Microsphere of Irbesartan.

The polymer concentration plays a crucial role in determining the rate of drug release from floating microspheres of Irbesartan. It has been observed that as the drug polymer ratio increases from 1:1 to 1:3, the release of the drug in microspheres decreases. Additionally, this study also found that the release of the drug decreases with an increase in the concentration of Ethyl cellulose, while it increases with an increase in the concentration of Eudragit S100. The addition of βCD in all developed formulations has shown to enhance the solubility and dissolution of Irbesartan, which is consistent with the previously reported results by Kumar (2010). These findings highlight the significant improvement in the dissolution rate of Irbesartan achieved by incorporating βCD in microspheres.

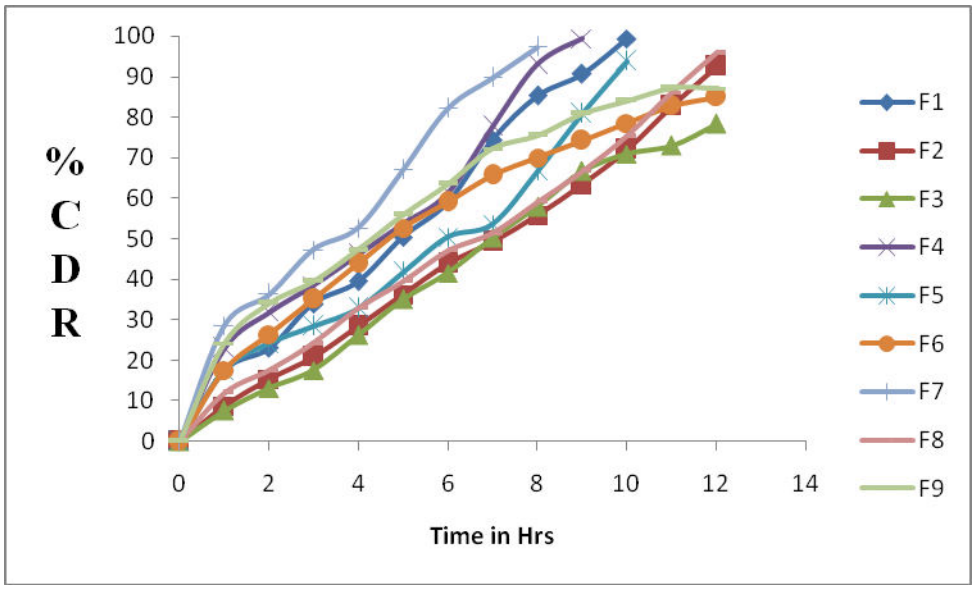


Fig. 6: Comparative *in vitro* dissolution profiles of Irbesartan floating Microspheres batches F1-F9.

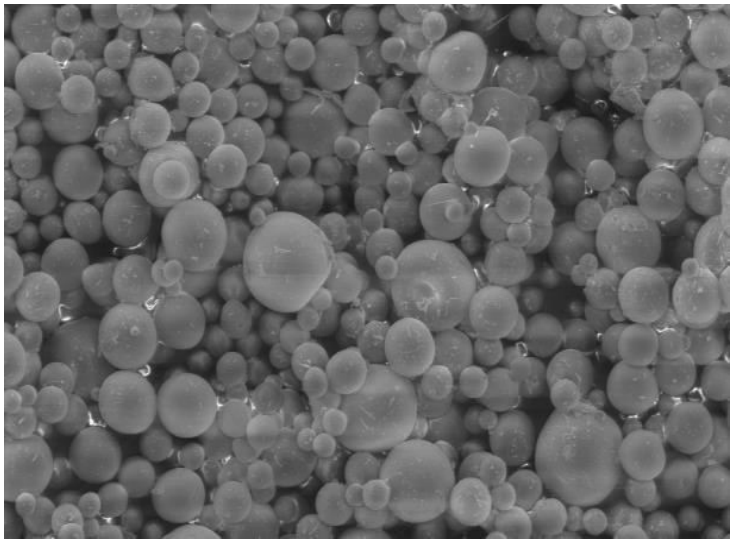


Fig. 7: SEM photographs of developed Irbesartan floating microspheres 400 X.

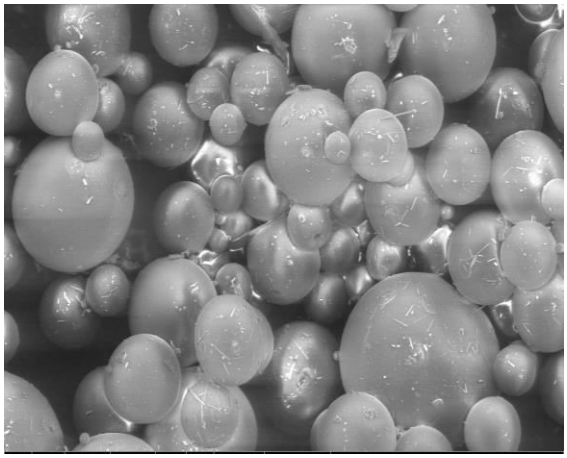


Fig. 8: SEM photographs of developed Irbesartan floating microspheres 1000 X.

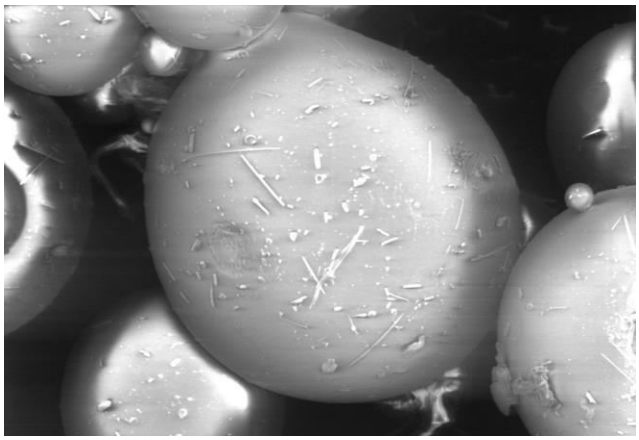


Fig. 9: SEM photographs of developed Irbesartan floating microspheres 2500 X.

The SEM microphotographs were taken at different magnifications it showed that showed that microspheres were found to be discrete, free flowing and rough surface and it exhibited a range of sizes. The SEM Figures 10 and 11 reveal that Irbesartan floating microsphere had a perfectly spherical appearance.

In vivo Study:

The optimized formulation F8 was chosen for the in vivo study, which was conducted on Albino rabbits using X-ray imaging technique. Based on radiological evidence, it can be inferred that the formulated F8 had a floating duration of more than 8 hours in the rabbit's stomach. Therefore, it can be concluded that the developed floating microsphere exhibits satisfactory floating properties in the rabbit's stomach.

For the best formulation F8 the R^2 value of Zero order model is 0.9968 (nearer to 1) which is dominant than the other models. As the diffusion exponent (n) showed values 0.8521 release of drug follows erosion swelling both mechanism

Stability Study:

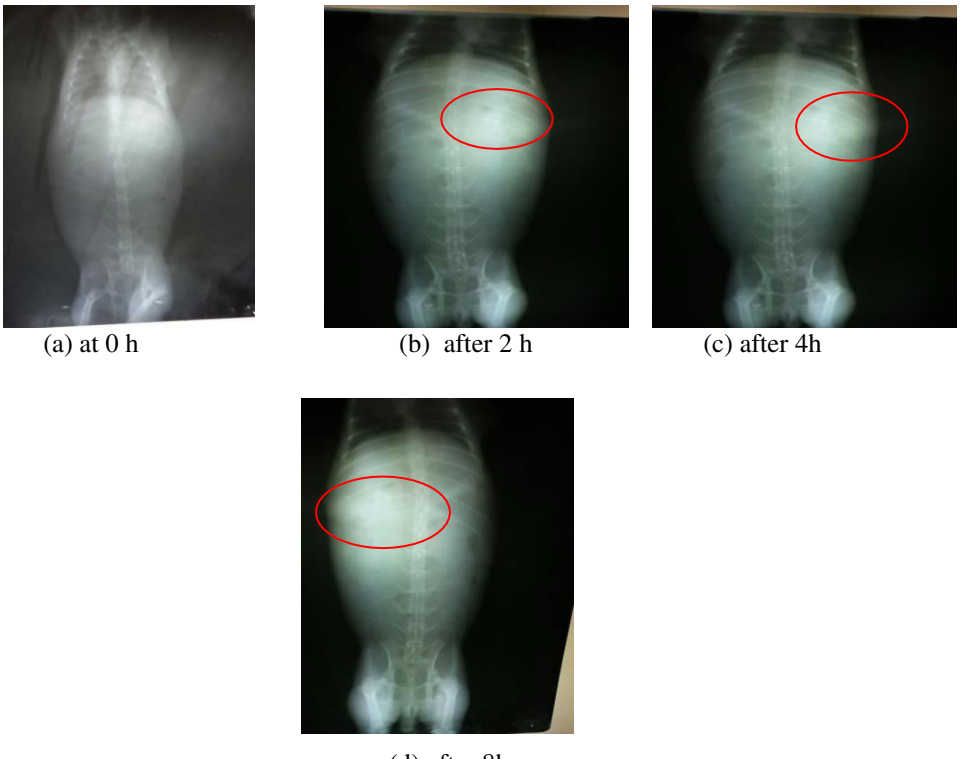
The long-term stability of the optimized F8 formulation was assessed through stability studies conducted in accordance with the ICH guidelines. The formulation was tested for % Practical yield, Buoyancy, DEE, DLE, and *in vitro* drug release. These studies were carried out at a temperature of 40±2°C and a relative humidity of 75±5% for a duration of six months, which served as an accelerated testingcondition. After storage for six months, analysis of the dissolution data revealed no significant alteration in the release pattern. Furthermore, all the evaluated parameters

Table 8: Comparison between the experimental and predicted values for the most probable Optimal formulation (F8)

Dependent variable	Optimized Formulation F8	
	Experimental	Predicted
% Practical Yield	81.11	79.43
% Buoyancy	73.95	74.21
% Entrapment Efficiency	81.43	85.44

Table 9: Kinetic Parameters of Floating Microsphere Batches F1-F9

Batch Code	Zero order (R2)	First order (R2)	Matrix	Korsmeyer Pappas (R2)	n (Release exponent)	Hixon-Crowell
F1	0.9949	0.8182	0.9411	0.9868	0.8031	0.9345
F2	0.9927	0.8821	0.9052	0.992	0.9489	0.9379
F3	0.9956	0.9762	0.9263	0.9955	1.0025	0.9885
F4	0.9825	0.7958	0.9503	0.9769	0.6716	0.9145
F5	0.9838	0.8551	0.9227	0.9682	0.7175	0.9223
F6	0.9416	0.9985	0.9987	0.9978	0.6596	0.996
F7	0.9699	0.91	0.9757	0.9813	0.6184	0.9708
F8	0.9968	0.8637	0.9302	0.9937	0.8521	0.9384
F9	0.9023	0.9955	0.9941	0.9951	0.554	0.9878



(a) at 0 h (b) after 2 h (c) after 4h

(d) after 8h

Fig. 10: X-ray photographs of floating microsphere of Irbesartan batch F8 at different time intervals (a) at 0 h; (b) after 2 h; (c) after 4h; (d) after 8 h.

Table 10: Stability study of optimized batch F8

Parameters	% Practical yield	%Buoyancy	% DEE	DLE (%)	Drug release (%)
Before storage	81.11±4.2	73.98±7.8	86.45±2.6	21.44±1.31	95.79±2.71
After storage	80.44±1.23	72.09±2.5	85.90±2.33	21.89±0.55	94.65±2.3

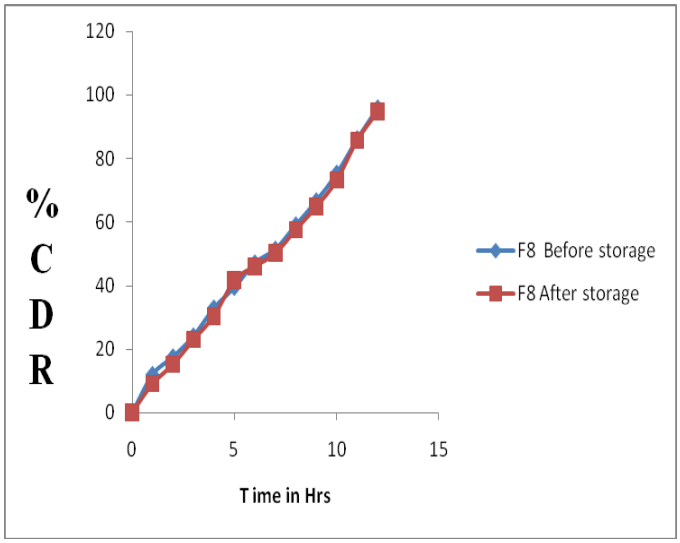


Fig. 11: Comparative dissolution profile of batch F8 before and after stability study.

remained comparable to their initial values.

Conclusion

It can be inferred that the Solvent Evaporation method was utilized to create Floating Microspheres of Irbesartan. The Irbesartan Floating Microspheres in formula F8 exhibited favorable drug release profiles and demonstrated prolonged action until the end of the 24th hour. This improvement in patient compliance and increased bioavailability offers a superior approach. The outcomes of the experimental design formulations and the kinetic modeling of the drug release study indicated that formulation F8 met all the desired criteria, making it the chosen optimized formulation for further in vivo study.

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