

## RESEARCH ARTICLE

# Statistically Optimized Repaglinide-loaded Floating Microspheres for the Gastric Sustained Delivery via Central Composite Design

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## ABSTRACT

Repaglinide (RPD) is a short-acting insulin secretagogue widely prescribed for the treatment of type 2 diabetes. In this study, RPD loaded ethyl cellulose/hydroxypropylmethylcellulose (EC/HPMC) floating microspheres (FM) have been formulated for gastric sustained release and improved bioavailability of RPD. Floating microspheres were prepared by oil in water emulsion solvent evaporation technique. A three levels Central-composite design (CCD) was applied to investigate the influence of different formulation components and process variables on the formulation responses and indicate the optimum using the numeric approach through the Minitab<sup>®</sup> software. All the formulations were characterized for entrapment efficiency (EE), production yield (PY) and in vitro buoyancy; the results were supported with the ANOVA analysis, three-dimensional contour graphs and regression equations. The optimal formulation showed a production yield of 81.72%, entrapment efficiency of 74.96% and buoyancy of 76.30%. Optical microscopy revealed the spherical shape of RPD floating microspheres with a mean particle size of  $24.60 \pm 1.19 \mu\text{m}$ . The floating microspheres are physically and chemically stable as confirmed through Fourier transform infrared spectroscopy (FTIR). The microspheres provided a sustained release of the RPD for more than 24 hours in simulated gastric fluid, following Korsmeyer-Peppas with non-fickian diffusion. The results indicate that the optimized floating microspheres can be a potential drug delivery system for the delivery of RPD in the stomach.

**Keywords:** Central composite design, Floating microspheres, Gastric sustained release, Repaglinide.

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## INTRODUCTION

Repaglinide is a widely prescribed, short-acting insulin secretagogue that is both safe and efficacious. It targets one of the major defects of T2D by promoting early-phase postprandial insulin secretion, lowering the blood glucose level.<sup>1</sup>

The oral controlled release drug delivery system has some limitations related to gastric emptying time. Too rapid and variable gastric emptying can result in incomplete release of the drug from the dosage form within the absorption window, resulting in poor bioavailability of the administered dose.<sup>2</sup>

Gastroretentive systems can remain in the gastric region for several hours, thus significantly prolong the gastric residence time of the drug. Prolonged gastric retention improves the solubility of drugs (which are less soluble in a high pH environment), reduces drug wastage, and improves bioavailability.<sup>3</sup>

Floating microspheres are gastro-retentive low-density systems based on a non-effervescent approach. Hollow microspheres are empty spherical particles without a core. Biodegradable microspheres incorporating a drug dispersed or dissolved in the particle matrix have the potential to release drugs in a controlled manner after floating on the gastric content.<sup>4</sup>

Product and process development problems in the pharmaceutical industry usually involve a number of independent variables which are characterized by multiple objectives. Statistically valid experimental design using surface response parameters can be employed to optimize data in order to provide an economical and effective formulation.<sup>5</sup>

The present study aimed to design and optimized the RPD loaded EC/HPMC floating microspheres by oil in water emulsion solvent evaporation method using a Minitab<sup>®</sup> statistical tool. The effect of independent variables was accessed on the

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various responses such as entrapment efficiency, production yield and *in-vitro* buoyancy to obtain the optimized RPD-loaded floating microspheres. Furthermore, the optimized floating microspheres were characterized by different physicochemical properties.

## MATERIALS AND METHODS

### Materials

Repaglinide was gifted by the National laboratory for the control of pharmaceutical products (LNCPP-Algeria). HPMC K4M was a gift from LDM group-Algeria. Ethylcellulose (viscosity 22cP, 48% ethoxyl), Polyvinylalcohol (87–90% hydrolyzed, average mol wt. 30.000–70.000) and dialysis bags (cut-off 12 kDa) were procured from Sigma Aldrich, USA. All the solvents, including dichloromethane (DCM), ethanol, methanol, and hydrochloric acid (HCl) used, were of analytical grade. Freshly prepared double distilled water was used throughout the experiment. All other ingredients used were of analytical grade.

### Preparation of Floating Microspheres

The RPD loaded EC/HPMC floating microspheres were prepared by the oil in water emulsion solvent evaporation method. The RPD mass was kept constant in all formulations (10 mg) while the mass of polymers was varied, as suggested by the Central composite design. The internal phase was prepared by dissolving the RPD, EC and HPMC in 5 mL of a mixture of DCM and ethanol (v:v, 1:1) under stirring. The aqueous phase was prepared by dissolving the PVA in 50 mL of distilled water. The internal phase was added in a dropwise manner in the aqueous phase. The microsphere suspension is obtained after evaporation of the organic solvents under mechanical stirring at room temperature for 2 hours. The floating microspheres are recovered by vacuum filtration (0.45  $\mu\text{m}$ ) and rinsed with double distilled water.<sup>6</sup> The filtrate was kept for drug assay as described later.

### Characterization of Floating Microspheres

#### Production Yield (PY)

The production yield is determined after weighing the floating microspheres dried at 40°C<sup>7</sup> by the following method:

$$PY = \frac{\text{Weight of the floating microspheres}}{\text{Initial weight of feeding drug and polymers}} \times 100 \quad (1)$$

#### Entrapment Efficiency (EE)

For measuring drug entrapment efficiency, the filtrate of the suspension of the floating microspheres was diluted by methanol and examined to determine the amount of non-encapsulated RPD after analysis by UV-visible spectroscopy (Shimadzu UV-1601, Japan) at 244 nm.<sup>8</sup> Entrapment efficiency (EE) was calculated as follows:

$$EE = \frac{\text{Initial weight of feeding drug} - \text{Weight of not encapsulated drug in filtrate}}{\text{Initial weight of feeding drug}} \times 100 \quad (2)$$

### *In-vitro* Buoyancy

The microspheres were spread over the beaker's surface, filled with 100 mL of simulated gastric fluid (HCl, pH=1.2) and agitated at 50 rpm for 8 hours.

The floating and the settled portions of the floating microspheres were recovered separately, dried and weighed. All experiments were performed in triplicate. Buoyancy was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres<sup>9</sup> as follows:

$$\text{Buoyancy (\%)} = \frac{Q_f}{Q_f + Q_s} \times 100 \quad (3)$$

Where  $Q_f$  and  $Q_s$  are the weights of the floating and the settled microspheres, respectively.

### Fourier Transform Infrared Spectroscopy (FT-IR)

The RPD, EC, HPMC powders and the optimal formulation of the floating microspheres are analyzed by FT-IR spectrophotometry ((JASCO, FT/IR-4600, USA) at room temperature between 400 and 4000  $\text{cm}^{-1}$  to reveal any possible chemical interaction between the polymers and RPD after the formulation of floating microspheres.

### Size and Morphology

The size and morphology of the optimal formulation of the floating microspheres were observed by an optical microscope (Oxion-euromex). The powder of the FM from drying after filtration is deposited on a glass slide and covered by a lamella. The morphology is observed and the mean size of 100 microspheres is calculated.<sup>10</sup>

### *In-vitro* Dissolution

The *in-vitro* dissolution study was performed in a water bath shaker (Memmert, Germany) at 50 rpm and a temperature of 37°C  $\pm$  0.5. In cellulose dialysis bags, the powder of the optimal FM formulation containing a predetermined mass of RPD is diluted with hydrochloric acid (HCl, pH = 1.2), then was immersed in beaker containing 500 mL of simulated gastric fluid (HCl, pH = 1.2) which is the dissolution medium used in this study. Three milliliters of the dissolution medium are taken at each time interval and analyzed by UV-visible spectrophotometry to quantify the RPD released. Sink condition was maintained by replacing 3 mL of fresh dissolution medium when each time of withdrawal of the sample for analysis.

### Kinetics of Drug Release

To investigate the mode of release from floating microspheres of RPD, the release data were analyzed with the following drug release kinetic approaches such as zero-order plot, first-order plot, Higuchi plot, Korsmeyer-Peppas plot. The approximation accuracy of individual models was assessed in terms of correlation coefficient ( $R^2$ ) values.<sup>11</sup>

**Table 1:** Levels of independent and dependent variables in CCD

Independent variables	Real and coded values of levels				
	- $\alpha$	-1	0	+1	+ $\alpha$
X <sub>1</sub> : Mass Ratio of EC/HPMC (%)	69.25	71.42	74.59	77.77	79.93
X <sub>2</sub> : Mass Ratio of RPD/EC+HPMC (%)	73.29	75.00	77.50	80	81.70
X <sub>3</sub> : PVA concentration (%)	0.36	0.40	0.45	0.50	0.53
<b>Dependent variables</b>	<b>Desired outcomes</b>				
Y1: Production yield (PY%)	Maximize (50–90)				
Y2: Entrapment efficiency (EE%)	Maximize (50–80)				
Y3: <i>In-vitro</i> buoyancy	Maximize (50–90)				

**Table 2:** Observed responses in CCD

Batch	Dependent variables			Independent variables			D
	X <sub>1</sub> (%)	X <sub>2</sub> (%)	X <sub>3</sub> (w/v %)	Y <sub>1</sub> (%)	Y <sub>2</sub> (%)	Y <sub>3</sub> (%)	
1	71.42	75.00	0.40	64.76	55.14	60.18	0.308
2	77.77	75.00	0.40	74.10	55.64	65.08	0.448
3	71.42	80.00	0.40	68.64	63.06	62.85	0.536
4	77.77	80.00	0.40	77.41	64.00	68.66	0.671
5	71.42	75.00	0.50	61.93	63.49	55.96	0.329
6	77.77	75.00	0.50	82.02	64.74	61.01	0.579
7	71.42	80.00	0.50	71.01	65.05	60.94	0.500
8	77.77	80.00	0.50	78.41	69.82	64.07	0.713
9	69.25	77.50	0.45	69.76	62.35	55.60	0.360
10	79.93	77.50	0.45	82.37	68.57	67.70	0.685
11	74.59	73.29	0.45	64.18	63.37	63.20	0.470
12	74.59	81.70	0.45	73.27	71.01	76.55	0.750
13	74.59	77.50	0.36	63.21	51.01	70.94	0.186
14	74.59	77.50	0.53	69.45	62.15	57.20	0.404
15	74.59	77.50	0.45	67.26	58.97	62.20	0.374
16	74.59	77.50	0.45	68.24	58.41	63.36	0.374
17	74.59	77.50	0.45	68.31	53.02	64.43	0.374
18	74.59	77.50	0.45	66.21	52.46	61.37	0.374
19	74.59	77.50	0.45	65.54	57.35	63.70	0.374
20	74.59	77.50	0.45	65.09	57.66	62.39	0.374

**Table 3:** Release kinetics data for optimized floating microspheres

Model	Zero order	First order	Higuchi	Korsmeyer-Peppas
R <sup>2</sup>	0.72	0.38	0.92	0.93 n=0.48

**Central Composite Design**

RPD-loaded floating microspheres were prepared according to a Central composite design using Minitab<sup>®</sup> software to study the effect of different variables on FM properties (Table 1).

The factors evaluated in this investigation were the mass ratio of EC/ HPMC (X<sub>1</sub>:  $\frac{m_{EC}}{m_{HPMC}+m_{EC}} \times 100$ ), the mass ratio of RPD/ EC+HPMC (X<sub>2</sub>:  $\frac{m_{EC}+m_{RPD}}{m_{HPMC}+m_{EC}+m_{RPD}} \times 100$ ) and the PVA concentration (X<sub>3</sub>: w/v %) with different levels for each factor as described in Table 1 (coded and real values). The evaluated responses were the production yield (Y1), the entrapment efficiency (Y2), and the *in-vitro* buoyancy (Y3).

The data and factors levels of CCD are presented in Table 2. The quadratic non-linear model generated by design is in the following form:

Where:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_{11}X_1^2 + A_{22}X_2^2 + A_{33}X_3^2 + A_{12}X_1X_2 + A_{13}X_1X_3 + A_{23}X_2X_3 \quad (4)$$

- Y: the measured response
- A<sub>0</sub>: the intercept
- A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub>: the linear regression coefficients
- A<sub>12</sub>, A<sub>13</sub>, A<sub>23</sub>: the interactive regression coefficients
- A<sub>11</sub>, A<sub>22</sub>, A<sub>33</sub>: the quadratic regression coefficients
- X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>: the studied factors
- X<sub>1</sub><sup>2</sup>, X<sub>2</sub><sup>2</sup>, X<sub>3</sub><sup>2</sup>: the quadratic effects
- X<sub>1</sub>X<sub>2</sub>, X<sub>1</sub>X<sub>3</sub>, X<sub>2</sub>X<sub>3</sub> represent the interaction between the variables.<sup>12</sup>

An analysis of variance (ANOVA) was performed to establish the optimum conditions.

The desirability function method was used to select the desirable optimum region, wherein the desired outcomes for choosing an optimum formulation were further narrowed as shown in Table 1. The responses  $Y_1$ ,  $Y_2$  and  $Y_3$  are initially transformed into individual desirabilities  $d_1$ ,  $d_2$  and  $d_3$  that vary over the range  $0 \leq (d_1, d_2, d_3) \leq 1$ . For all responses, the individual desirabilities should be maximized as follow:

$$d_1, d_2, d_3 = \left( \frac{Y_i - Y_{\min}}{Y_{\max} - Y_{\min}} \right) \quad (5)$$

Where,

$Y_{\max}$ ,  $Y_{\min}$  are the upper and lower acceptable values of response. The overall desirability value ( $D$ ) is calculated by the following equation:

$$D = \sqrt[3]{d_1 \times d_2 \times d_3} \quad (6)$$

## RESULTS AND DISCUSSION

### Central Composite Design

The results of the central composite design were assessed for  $R^2$ , adjusted  $R^2$ , p-values of the model as quality indicators for the model.

### Production Yield

The production yield of all the selected 20 formulations was in the range 61.93–82.37% depending upon the variation in the independent variables. ANOVA analysis indicates that there was a significant effect of various independent variables on production yield. The quadratic equation of the selected model ( $R^2 = 0.92$ ,  $R^2_{\text{ajus}} = 0.84$ ) indicating the effect on above mentioned variables is given below.<sup>7</sup>

$$Y_1 = 66.72 + 4.89 X_1 + 2.04 X_2 + 1.83 X_3 + 3.64 X_1^2 - 1.04 X_2^2 + 0.20 X_3^2 - 1.56 X_1 X_2 + 1.17 X_1 X_3 - 0.21 X_2 X_3 \quad (7)$$

The statistical analysis indicates that there was a significant increase in the production yield ( $Y_1$ ) of the floating microspheres with an increase in the polymers concentration ( $X_2$ ) (p-value= 0.000) and especially the EC comparing with HPMC ( $X_1$ ) (p-value= 0.009) while the concentration of PVA ( $X_3$ ) has no significant effect (p-value= 0.055) on the production yield as indicated by the positive coefficients in the regression equation (Eq 7) respectively.

From the Response surface plot (Figure 1), it was evident that the RPD to polymers ratio ( $X_2$ ) has a positive effect on the production yield of the FM. With increase in the drug-to-polymers ratio, the production yield also increases. This effect can be explained by the increase throughput of the polymer slurry and rapid evaporation of the solvent.<sup>14</sup>

The product yield depended upon the polymers ( $X_1$ ) used for the formulation of FM. The yield of the microspheres containing less HPMC and more EC polymers was found to be increased. This may be due to the migration of HPMC into

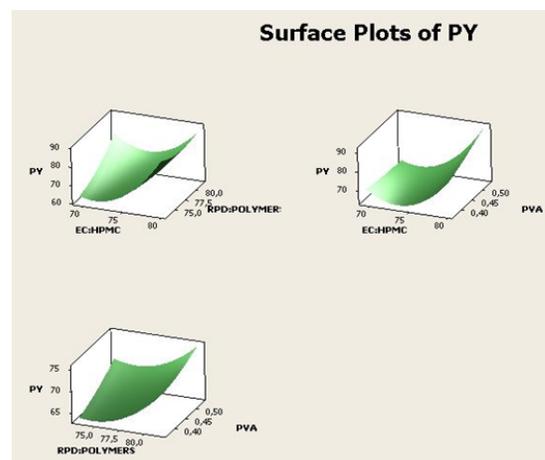


Figure 1: Response surface plot of the production yield of the floating microspheres

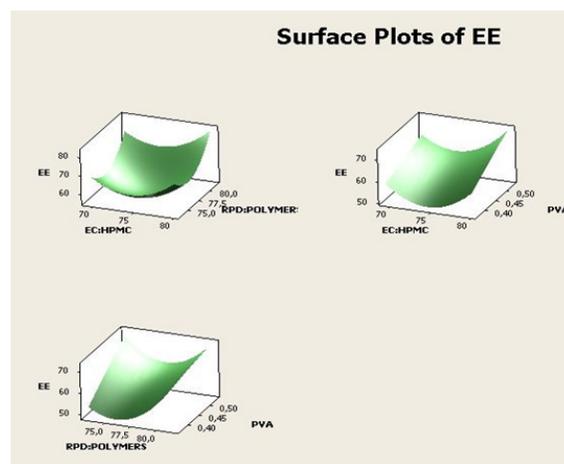


Figure 2: Response surface plot of the entrapment efficiency of the floating

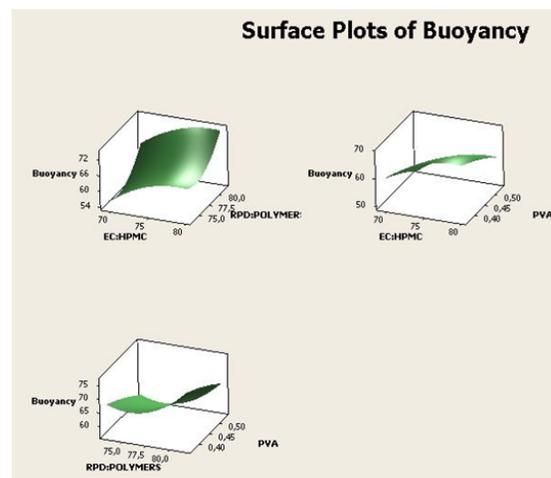


Figure 3: Response surface plot of the *in-vitro* buoyancy of the floating microspheres

continuous phase forming agglomerates accompanied with sticking of the polymer to the stirrer blade and beaker surface.<sup>15</sup>

### Entrapment Efficiency

The indirect method has been adopted to find out the percent EE of RPD in the microspheres. The response surface plot (Figure 2) indicates the effect of three independent variables on the EE of prepared microspheres. Formulation 12 showed maximum entrapment of RPD (71.01%) while formulation 13 showed minimum encapsulation of RPD (51.01%). ANOVA analysis indicates that there was a high positive significant effect of the RPD: polymers ratio ( $X_2$ ) (p-value = 0.001) and the concentration of PVA ( $X_3$ ) (p-value = 0.000) on RPD entrapment efficiency while the effect of EC:HPMC ratio ( $X_1$ ) is insignificant on the EE of the RPD (p-value = 0.051).

The quadratic equation of the selected model ( $R^2=0.92$ ,  $R^2_{\text{ajus}}=0.85$ ) indicating the effect on above mentioned variables is given below.

$$Y_2 = 56.33 + 1.31 X_1 + 2.61 X_2 + 3.22 X_3 + 3.05 X_1^2 + 3.66 X_2^2 - 0.08 X_3^2 + 0.49 X_1 X_2 + 0.57 X_1 X_3 - 1.20 X_2 X_3 \quad (8)$$

It has been observed that the EE of the microspheres has been increased with an increase in the concentration of the polymers in the formulation ( $X_2$ ). This may be because, at higher concentration of polymers, the drug available will be surrounded by excess of polymer and resulting in better entrapment.<sup>8</sup>

The entrapment efficiency improved with increasing concentration of PVA ( $X_3$ ) in the formulations. Increasing amount of PVA might have increased the viscosity of internal phase by arranging themselves in layers around the emulsion droplets. This conformation may have restricted the escape of Repaglinide until the droplets converted into floating microspheres.<sup>16</sup>

### In-vitro buoyancy

*In-vitro* buoyancy was determined for individual formulations; the *in-vitro* buoyancy of all the selected 20 formulations was in the range 55.60–76.55%. ANOVA analysis indicates that there was a high positive significant effect of the EC:HPMC ratio ( $X_1$ ) (p-value = 0.001), and RPD: polymers ratio ( $X_2$ ) (p-value = 0.001), while the concentration of PVA ( $X_3$ ) (p-value = 0.001) has a high negative significant effect on the buoyancy of FM.

$$Y_3 = 63 + 2.87 X_1 + 2.69 X_2 - 2.77 X_3 - 1.07 X_1^2 + 1.83 X_2^2 - 0.22 X_3^2 \quad (9)$$

The variation in the buoyancy of FM corresponds to different independent variables was explained by the given second order equation ( $R^2=0.83$ ,  $R^2_{\text{ajus}}=0.76$ ) (Eq 9) and presented by response surface plot in Figure 3.

The *in-vitro* buoyancy of microspheres can be correlated to low density and insolubility of polymers in the simulated gastric fluid (pH 1.2). The buoyancy of particles depends on their density and size. The size of microspheres exhibited an inverse relationship to the microsphere density. Hence,

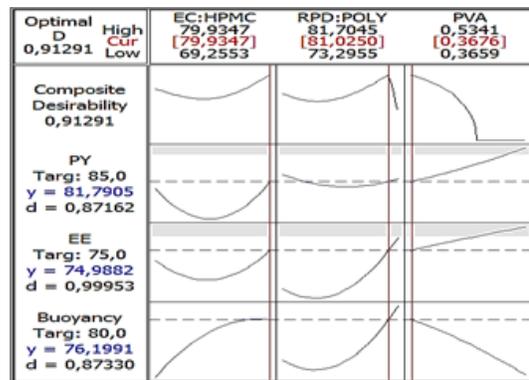


Figure 4: Optimum levels of factors and responses of the floating microspheres

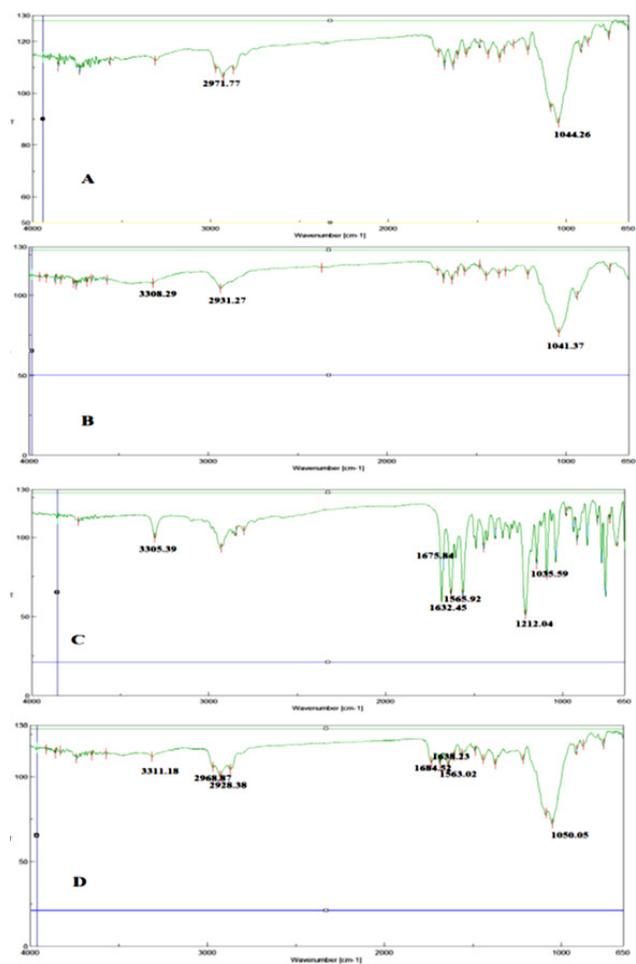
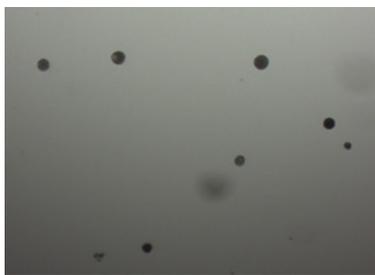


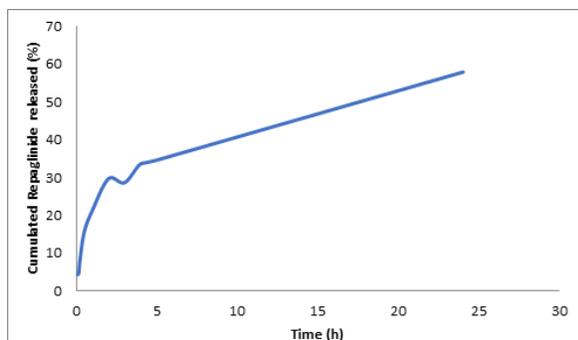
Figure 5: FT-IR spectra of Ethylcellulose (A), hydroxypropylcellulose (B), Repaglinide (C), Repaglinide loaded floating Microspheres (D)

the buoyancy of microspheres increased with an increase in particle size, which can be directly related to the increase in the polymers concentration. The particles with a higher polymers ratio are less dense and more buoyant.<sup>17</sup>

The formulations containing higher amounts of ethyl cellulose ( $X_1$ ), showed a more buoyancy that was due to



**Figure 6:** Optical microscope image of the optimized floating microspheres



**Figure 7:** *In-vitro* release profile of repaglinide loaded floating microspheres

the rapid penetration of the processing medium in the microspheres.<sup>15</sup>

Buoyancy of the FM decrease with an increase in PVA concentration ( $X_3$ ). The buoyancy could have decreased due to the tightening of polymeric network, leading to microsphere shrinkage with an increase in the concentration of emulsifier.<sup>18</sup>

### Optimization

The desirability approach has been employed for the selection of optimized formulation.

For the optimized formulation, the predicted maximum values of the responses are PY= 81.79%, EE= 74.98% and buoyancy = 76.19% along with individual desirability of 0.87, 0.99 and 0.87, respectively. The overall desirability has a value of 0.91 with factors setting at 79.93% for the EC:HPMC ratio, 81.02% for RPD:EC+HPMC ratio and 0.36% for the PVA concentration (Figure 4).

### Fourier Transform Infrared

The characteristic absorption peaks of EC are presented by the following bands: 2971.77  $\text{cm}^{-1}$  (C–H stretching) and 1044.26  $\text{cm}^{-1}$  (C–O–C stretching).<sup>19</sup>

For the HPMC, the absorption peaks are obtained at: 3308.29  $\text{cm}^{-1}$  (OH stretching), 2931.27  $\text{cm}^{-1}$  (C–H stretching), and 1041.37  $\text{cm}^{-1}$  (C–O–C stretching).<sup>20</sup>

The repaglinide IR spectrum showed absorption peaks at: 3305.39  $\text{cm}^{-1}$  (N–H stretching), 1675.84  $\text{cm}^{-1}$  (C=O stretching), 1632.45  $\text{cm}^{-1}$  (aromatic N–H stretching), 1565.93  $\text{cm}^{-1}$  (aromatic C = C stretching), 1212.04  $\text{cm}^{-1}$  and 1035.59  $\text{cm}^{-1}$  (C–O stretching).<sup>21</sup>

The IR spectrum of the optimal formulation of the FM showed various intact peaks of RPD, EC, and HPMC at 3311.18  $\text{cm}^{-1}$ , 2968.87  $\text{cm}^{-1}$ , 2928.38  $\text{cm}^{-1}$ , 1684.52  $\text{cm}^{-1}$ , 1638.23  $\text{cm}^{-1}$ , 1563.02  $\text{cm}^{-1}$  and 1050.05  $\text{cm}^{-1}$  respectively, suggesting the compatibility of various components and lack of any interaction among them (Figure 5).

### Size and Morphology

The Figure 6 shows that the optimal formulation of microspheres has a spherical shape with an average size of  $24.60 \pm 1.19 \mu\text{m}$ .

### *In-vitro* Release Kinetic Evaluation

The dissolution profile (Figure 7) shows a sustained release of RPD from the formulated FM, only 57.92% of the RPD was released over the 24 hours.

The results of the release kinetics are presented in Table 3; it shows that the R2 differ from one model to another. The optimized FM follow a korsmeyer-Peppas release model ( $R^2=0.93$ ). The n value (0.48) is superior to 0.45 indicating that the release follows a non fickian diffusion mechanism.<sup>22</sup>

### CONCLUSION

The optimized floating microspheres obtained via central composite design displayed a production yield of 81.79%, entrapment efficiency of 74.98% and buoyancy of 76.19%, a particle size of  $24.60 \pm 1.19 \mu\text{m}$  with a spherical shape, and a sustained drug release over a period of 24 hours governed by fickian diffusion mechanism with Korsmeyer-Peppas release kinetics. This study demonstrates that statistical experimental design methodology can optimize the formulation and process variables to achieve favorable responses.

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