INTRODUCTION

Oral drug delivery has been the most convenient route of administration since ages owing to its ease of administration and better patient compliance (Satish et al. 2010). However for many drugs the site of maximum absorption reside in upper gastrointestinal tract, such drugs shows low bioavailability either due to shorter residence time of dosage form in that area or due to incomplete release of the drug. Gastroretentive dosage forms provide us with new and important therapeutic options that prolong the gastrointestinal residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects (Nayak et al. 2010; Chein 1992).

Metoprolol tartrate (MT) is a cardioselective beta-adrenergic blocking agent used in the management of hypertension. Metoprolol has short half-life of 4-6 h which requires multiple daily dosing to maintain plasma concentration for better therapeutic response and patient compliance (Kendall et al. 1991; Aqil et al. 2007). It has also been reported that MT absorption in the duodenum and jejunum is directly proportional to the dose availability (Hirtz J 1985; Jobin et al. 1985).

Much work has been done on floating single unit dosage forms of drug but owing to its “all or none” emptying phenomenon there is variability in their transit time (Yeole et al. 2005; Baumgartner et al. 2000). In contrast, multiple-unit particulate dosage forms (e.g., microspheres) have the advantages that they pass uniformly though the gastrointestinal tract to avoid the variabilities of gastric emptying and provide an adjustable release, thereby reducing the inter subject variability in absorption and risk of local irritation (Yeole et al. 2005). Hence an attempt has been made to design a floating microparticulate system of metoprolol tartrate, using ethyl cellulose to improve the release profile of the drug and also target it to stomach and upper intestine via gastric retention. There are many formulation and process parameters that affect
the properties of microspheres. In the present study influence of such dependent and independent variables on formation of metoprolol floating microspheres was studied by using optimizing techniques like 2^3 full factorial designs and Box Behenken design (Narendra et al. 2006).

**MATERIALS AND METHODS**

Metoprolol tartrate was obtained as a gift sample from Astra Zeneca India Pvt. Ltd., Bangalore. Ethyl cellulose was procured as gift sample from Dow Chemical International Pvt. Ltd. Mumbai, India. Solvents like ethanol, dichloromethane; Tween 80 was purchased from S.D. Fine Chemicals, Mumbai, India. All other reagents used were of analytical grade, double distilled water was used though out the studies.

**METHODS**

**Formulation of floating microspheres by solvent evaporation method**

Floating microspheres were prepared by solvent evaporation method. The drug and polymer were weighed in different proportions and dispersed in a mixture of 20 ml of 1:1 v/v of ethanol and dichloromethane with vigorous agitation to form uniform drug polymer dispersion. This was slowly added to dispersion medium consisting of 0.25% v/v Tween 80 in 50 ml distilled water. The dispersion was constantly stirred using an overhead stirrer (Remi Equipments Pvt Ltd, Mumbai, India) at room temperature over a period of 2-3h, to ensure complete evaporation of solvent while checking for the formation spherical microspheres for every 30 m. Formed microspheres were filtered and washed with distilled water and dried for 24 h in dessicator and stored in tightly closed container.

**Experimental design for optimization of floating microspheres of metoprolol tartrate using 2^3 factorial design.**

A 2^3 factorial design was used to statistically optimize the formulation factors and evaluate main effects, interaction effects and quadratic effects on the amount of drug entrapped and on particle size. This gives information regarding the properties of microspheres. In the present study influence of such dependent and independent variables on formation of metoprolol floating microspheres was studied by using optimizing techniques like 2^3 full factorial designs and Box Behenken design (Narendra et al. 2006).

**Formulation and Evaluation of Floating Microspheres Using Factorial Design**

Optimized formulation was selected based on the data obtained for particle size and entrapment efficiency using 2^3 factorial designs. Probability factor, R^2 values and lack of fit values were determined to prove whether the design is significant or not. Formulation with narrow particle size distribution and highest drug entrapment was considered to be the optimized. The selected optimized formulation was then subjected to study the possible effect of other independent variables on the formation of floating microspheres. The aim was to know whether those variables would have any significant effect on the response like particle size and percent drug entrapment which we have studied using factorial design. Hence Box-Behenken design was opted to determine the response surface graphs to study the effect of variables on desired response effectively.

**Selection of the Optimized Formulation**

**To Determine the effect of Independent Variables on Optimized Formulation.**

Response surface graphs were plotted using Box- Behenken design. The effect of independent variables (Tween 80 and volume of disperse phase) on formation of microspheres was studied taking three factors at two different levels with triplicate centerpoint.

To determine the effect of Tween 80, these factors considered were ethyl cellulose (X1), Tween 80 (X2) and stirring speed (X3) at two levels, low and high (1-4 g), (0.25-1 %) and (800-1600) respectively. Similarly for determining the effect of volume of dispersed phase on dependent variables the factors selected were ethyl cellulose (X1), Disperse Phase (X2) and stirring speed (X3) at low and high levels, Ethyl cellulose (1-4 g), Dispersed phase (10-20 ml) and stirring speed (800-1600). The process parameters were varied at two different levels to find out the effect of the various independent variables. The total 15 runs with triplicate centre points were generated and the responses were determined. All the responses observed for 15 formulations prepared were simultaneously fitted to quadratic models using Design Expert®. Comparative values of R^2, SD, and % CV are given along with the regression equation generated for each response.

Responses like percent entrapment and particle size were determined. Quadratic equations, regression values were obtained to study the main effect and interaction of different variables on
Percent Buoyancy = \frac{Q_f - Q_s}{Q_f} 

Q_f = Weight of floating microspheres.  Q_s = Weight of settled microspheres

Percentage Buoyancy to determe the percentage buoyancy, 100 mg of microspheres were washed with 1 ml of distilled water. The absorbance of the filtrate was taken at 273.5 nm to estimate the unentrapped drug. To determe the incorporation efficiency 10 mg of drug loaded microspheres were solubilised in 10 ml of 1:1 ratio of ethanol and dichloromethane. The absorbance of the filtrate was taken at 274 nm with 1:1 ethanol and dichloromethane mix as blank. This gives total/ actual drug.

**Percent drug entrapment**

\[
\text{Percent drug entrapment} = \frac{\text{Actual drug} - \text{unentrapped drug} \times 100}{\text{Actual drug}}
\]

**In-vitro drug release**

Dose equivalent to 100 mg of floating microspheres (F4) was accurately weighed and dissolution studies were carried out using simulated gastric fluid (enzyme free) 900 ml at temperature 37± 0.5 °C using USP type II apparatus. The speed of rotation was maintained at 100. Aliquot of 5 ml of dissolution medium was withdrawn at predetermined time interval up to a period of 12 h and replaced with fresh medium. Content of metoprolol tartrate was determined by using UV spectrophotometer (Spectro UV 2080, Double beam, Analytical Technologies, India) at 274 nm against SGF as blank, dissolution studies were conducted in triplicate.

**RESULTS AND DISCUSSION**

**Formulation of floating microspheres by solvent evaporation method**

Parameters like different ratios of drug to polymer, stirring speed and volume of continuous phase were changed as predicted by the 2^3 factorial design and floating microspheres of metoprolol tartrate were formulated by solvent evaporation technique with different ratios as shown in the table 2.

<table>
<thead>
<tr>
<th>Run</th>
<th>Coded formulations</th>
<th>Factor 1 (A:Ethyl cellulose)</th>
<th>Factor 2 (B:RPM)</th>
<th>Factor 3 (C:Continuous phase)</th>
<th>Response 1 (Percent Drug entrapment)</th>
<th>Response 2 (Particle size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
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<td>800</td>
<td>50</td>
<td>36</td>
<td>124</td>
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</tbody>
</table>

**Fitting the Model to the Data**

Total 19 runs with triplicate centre points were generated and the responses so observed are shown in Table 2. The response ranges of Y1 and Y2 for all batches were 16-77%, and 56-184 µm respectively.
The model F-value of 13.29 implies the model is significant \( (p < 0.0001) \). The lack of fit F-value of 0.0004 implies the lack of fit is significant \( (p = 0.0063) \). In this case X2, X3, XI X2, XIX3 and X2X3 are significant model terms and X1 (ratio of ethyl cellulose) had a more pronounced effect on percent entrapment and particle size. Stirring rate (X2) and Volume of continuous phase (X3) have lesser effect than that with ethyl cellulose (X1). The predicted \( R^2 \) of 0.8931 is in reasonable agreement with the adjusted \( R^2 \)-squared of 0.8647 (Table 3). Adequate precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 5.587 indicates an adequate signal. Therefore this model is significant and can be used to navigate the design space.

In the study it was revealed that the responses (Y1) was found to be significantly higher (Y1, 77) only when ethyl cellulose was used at higher concentration and rpm and continuous phase at 1600 and 50 ml respectively for F4 formulation. The responses of these formulations ranged from a low drug entrapment of 16% (F10, at low levels of ethyl cellulose, rpm and continuous phase) to a higher drug entrapment of 77% (F4, at higher levels of ethyl cellulose, rpm and lower levels of continuous phase). Percentage drug entrapped increased with increase in concentration of the polymer (+1 level) as the polymer is available in surplus amount to entrap high amount of drug.

Table 3 Results of regression analysis for responses Y1 and Y2.

<table>
<thead>
<tr>
<th>Quadratic model</th>
<th>R²</th>
<th>Adjusted R²</th>
<th>Predicted R²</th>
<th>Adequate Precision</th>
<th>SD</th>
<th>C.V. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (Y1)</td>
<td>0.8568</td>
<td>0.8647</td>
<td>0.8931</td>
<td>8.386</td>
<td>8.56</td>
<td>22.43</td>
</tr>
<tr>
<td>Response (Y2)</td>
<td>0.7401</td>
<td>0.7215</td>
<td>0.6605</td>
<td>8.929</td>
<td>21.02</td>
<td>17.51</td>
</tr>
</tbody>
</table>

Response Analysis though Polynomial Equations

Response 1 (Y1) Percent entrapment

From values of probability factor, \( R^2 \) and lack of fit values it was clear that the model was significant. Quadratic equation gives information regarding effect of variables either individually and also in combination. In a polynomial equation of significant model, the positive coefficient of a factor show that it has a positive effect and a negative coefficient of factor show a negative effect on the response.

The model proposes the following polynomial equation for percent drug entrapment.

\[
Y1 = 38.19 + 13.19X1 + 3.69X2 - 3.31X3 + 6.94X1X2 + 0.44X1X3 - 0.31X2X3
\]

Where, \( Y1 \) percent entrapped, \( X1 \) is the polymer concentration, \( X2 \) is the stirring speed and \( X3 \) is the continuous phase volume. The model F-value of 13.29 implies the model is significant \( (p < 0.0001) \). The lack of fit F-value of 0.0004 implies the lack of fit is significant \( (p = 0.0063) \). In this case X2, X3, XI X2, XIX3 and X2X3 are significant model terms and X1(ratio of ethyl cellulose) and X2(stirring speed) had a more pronounced effect than X3(continuous phase)on percent entrapment and particle size.

From the equation quadratic equation, the positive coefficients for polymer concentration and stirring speed show that with increase in these factors the percent entrapment increased. This is because, at higher concentration of polymer, the drug available will be surrounded by excess of polymer and resulting in better entrapment. Similar effect with increase in stirring rate was observed because at higher speed the shearing stress will be more, drug and polymer will be distributed evenly thus making the polymer to entrap the drug in higher amounts.

The negative coefficient for factor X3 shows that with increase in continuous phase volume the percent entrapment decreased. This is because of slow diffusion of drug into continuous phase.

Response 2 (Y2): Particle size

The following polynomial equation prevailed from the model for particle size of metoprolol tartrate floating microspheres.

\[
Y2 = 118.63 + 29.37X1 - 21.50X2 + 3.25X3 - 0.50X1X2 + 7.00X1X3 + 9.38X2X3 + 15.13X1X2X3
\]

A positive value for the coefficient is an indicative of the favourable effect whereas a negative value for the coefficient indicates an unfavourable effect of that particular factor on the response. In our study, it was revealed that the response, particle size (Y2) was found to be significantly higher (Y2, 184 \( \mu m \)) only when the ethyl cellulose was used at lower concentration, rpm and continuous phase volume were 800 and 100 ml respectively. The responses of these formulations ranged from a low particle size of 56 \( \mu m \) (F4, high level of ethyl cellulose, high level rpm and low level continuous phase) to a higher particle size of 184 \( \mu m \) (F10, low level of ethyl cellulose, low level rpm and high level continuous phase).

Positive coefficient for X1 show that with increase in concentration of polymer the particle size increased this is because there was no proportionate increase in amount of drug with polymer that we used, so the same amount of drug is present even at higher concentrations of polymer making excess polymer to surround the same amount of drug resulting in increase in particle size. The particle size decreased with increase in stirring speed this is because the higher shearing stress breakup the molecules to larger extent at higher stirring rates.

In case of response Y2 (particle size), X1 and X3 have positive effect that is with increase in concentration of polymer and continuous phase volume, particle size increases and negative coefficient for X2 show that with increase in stirring speed the particle size decreases. A negative coefficient for combined effect for factors X1X2 show that the combined effect is negative that is decrease in particle size.

Contour Plots and Response Surface Analysis

Two dimensional contour plots and thee dimensional response surface plots were prepared for the two responses are shown in Figures 1 and 2 for responses Y1 and Y2 respectively. An interaction effect of the factors on the responses is clearly evident from the plots.
Selection of the optimized formula

Form the values given in table 4 and 5 it is evident that the model is significant with significant p value (p < 0.0001), lack of fit value (p < 0.0063) and R² values. Formulation F4 was found to have narrow particle size range and better drug entrapment. Based on the these parameters F4 formulation was considered to be the optimized and carried further for studying the possible effect of other independent variable.

Table 4 Optimized formulation

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Ethyl cellulose (mg)</th>
<th>Stirring speed (rpm)</th>
<th>Continuous phase volume (ml)</th>
<th>Percent entrapment</th>
<th>Particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4</td>
<td>4</td>
<td>1600</td>
<td>50</td>
<td>77</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 5 Regression values (F4) for ethyl cellulose, Tween 80 and stirring speed.

<table>
<thead>
<tr>
<th>Responses</th>
<th>R-Squared</th>
<th>Adj R-Squared</th>
<th>Pred R-Squared</th>
<th>Adeq Precision</th>
<th>Std. Dev.</th>
<th>C.V. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>0.9883</td>
<td>0.9672</td>
<td>0.8412</td>
<td>25.355</td>
<td>3.79</td>
<td>7.54</td>
</tr>
<tr>
<td>Y2</td>
<td>0.9891</td>
<td>0.9695</td>
<td>0.9207</td>
<td>22.742</td>
<td>7.2</td>
<td>6.88</td>
</tr>
</tbody>
</table>

To Determine the effect of Independent Variables on F4 Formulation

Based on the above optimization, the effect of external as well internal parameter like concentration of surfactant and disperse phase (ethanol: dichloromethane) were studied as previously discussed in methodology. Responses obtained from all 15 formulations were simultaneously fitted to quadratic models using Design Expert®. Response surface graphs along with contour plots were plotted (Figure 3 and 4)

Quadratic Equations for Responses

Response Y1

Percent entrapment = 54.33+24.25X1+5.75X2+10.0X3-2.5X1X2+2.0X1X3+6.0X2X3-1.92X1²-4.92X2²-0.92X3²

Response Y2

Particle size = 84.67+43.00X1-12.38X2-23.88X3+0.25X1X2+11.25X1X3+5.50X2X3+22.17X1²-13.42X2²-1.92X3²

In quadratic equations for entrapment, the coefficient for parameter Tween 80 is positive that is with increase in concentration of Tween 80 the percent entrapment increases. It is negative for particles size, the particle size decreases with increase in Tween 80 concentration. And this is reflected in contour and 3D response graphs as shown in figure. The increase in percent entrapment and decrease in particles size is due to decrease in interfacial tension between drug and polymer. This leads to even distribution of drug among the polymer resulting in favourable effect.

Quadratic equations for responses

Response Y1

Percent entrapment = 44.0+15.12X1+5.75X2+10.38X3-2.00X1X2+4.75X1X3+8.00X2X3-0.12X1²+1.63X2²-2.63X3²

Response Y2

Particle size = 126.33-32.88X1-6.62X2-27.00X3+5.75X1X2-20.50X1X3+25.00X2X3+18.96X1²-9.54X2²-8.29X3²

In the equations for percent entrapment coefficient for the factor disperse phase (X2) is positive so the percent entrapment increases with increase in volume of disperse phase. And the particle size decreased with increase in volume of disperse phase. The polymer and drug are dispersed in disperse phase. Generally with increase in polymer ratio the percent entrapment increases, but in this case the increase in polymer concentration increases viscosity resulting increased particle size and lump formation.
Jinukula Bhavani, Shah Saloni and Dhurke Rajeshri, *Formulation and Evaluation of Floating Microspheres Using Factorial Design*

**Flow properties**

Data obtained for flow properties of various formulations are shown in Table 6. Flow properties were found to good for most of the formulations. Formulations with particle size less than 100 µm showed excellent flow properties as compared other formulations.

**Percent Yield**

Percentage yield of more than 75% was observed for all the formulations. With increase in polymer concentration increase in the percentage of floating microspheres was observed because formation of small and hollow microspheres.

**Floating Time**

Formation of hollow or porous microspheres makes the microspheres to float; floating time for F4 formulation was high when compared to other formulations with lesser proportions of polymer. Developed floating microspheres remained floating for a period of 12 h.

**Percentage Buoyancy**

Solvents like ethanol and dichloromethane evaporates very quickly making the polymer hollow and porous that makes the formulation to float for longer period of time. As polymer concentration increases porosity of the polymer is increased.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Formulation</th>
<th>Particle size (µm)</th>
<th>Percent Yield</th>
<th>Angle of repose (degrees)</th>
<th>C.I (%)</th>
<th>Hausner’s ratio</th>
<th>Percentage Buoyancy</th>
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<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>159±6.4</td>
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</tr>
<tr>
<td>2</td>
<td>F2</td>
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</tr>
<tr>
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<td>F3</td>
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<td>87±1.3</td>
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<td>1.10±0.1</td>
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<tr>
<td>4</td>
<td>F4</td>
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<tr>
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<td>F6</td>
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<td>8</td>
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<td>F15</td>
<td>74±1.9</td>
<td>84±1.7</td>
<td>27±0.8</td>
<td>0.9±0.07</td>
<td>93±4.4</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>F16</td>
<td>86±0.8</td>
<td>77±3.2</td>
<td>28±1.1</td>
<td>1.08±0.3</td>
<td>87±3.1</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>F17</td>
<td>131±4.2</td>
<td>85±1.9</td>
<td>36±0.5</td>
<td>1.27±0.13</td>
<td>87±2.9</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>F18</td>
<td>132±5.5</td>
<td>82±0.86</td>
<td>33±1.5</td>
<td>1.24±0.04</td>
<td>79±2.4</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>F19</td>
<td>124±3.3</td>
<td>79±1.6</td>
<td>33±0.7</td>
<td>1.21±0.11</td>
<td>89±1.7</td>
<td></td>
</tr>
</tbody>
</table>

**Percent drug Entrapment**

Percent drug entrapment was found to be high ie 77% for F4 formulation as compared to other formulations. Percent drug entrapment was found to be more when the polymer concentration was high, at optimum stirring rate of 1600. Sufficient polymer concentration is needed for getting uniform spherical microspheres with good drug entrapment. At low polymer concentration microspheres formed are not spherical. Stirring rate also plays a significant role in percent drug entrapment at very high stirring rate polymer forms lump while at low stirring rate no microspheres are formed.

**Characterization**

**Scanning Electron Microscopy**

Developed floating microspheres (F4) were found to be porous, spherical having smooth surface as evident in figure 5. The perforated microsphere were formed at high stirring speed of 1600 it may be due to the fact that rapid evaporation of solvent takes place which results in void formation. The high floating time of 12h obtained for formulation (F4) would be due to the porous structure of microspheres which makes the micropheres light weight and less dense.

**Particle size Analysis**

Particle size of floating microspheres varied among the formulation due to variation in the composition of formulations. The effect of polymer ratio on the particle size of microspheres is shown in Table 6. With increase in concentration of polymer the particle size increased this is evident from the quadratic equations. It is also seen that with increase in volume of continuous phase the particle size increased. Increase in Tween 80 concentration the particle size decreased because of decreased interfacial tension. As stirring speed increases from 800 rpm to 1600 rpm particle size decrease because shearing force will increase resulting in agitation breakup of bulk of polymer into fine droplets.

![Figure 3 Effect of Tween 80 on Percent entrapment (Y1) and Particle size (Y2)](image)

![Figure 4 Effect of Disper phase on percent entrapment (Y1) and Particle Size (Y2)](image)

![Figure 5 Scanning Electron microscopy image of optimized formulation F4](image)
In-vitro Drug Release

The dissolution profiles were compared among different formulation. Percentage drug release was increased with increase polymer concentration this may be due to decrease in particle size as shown in Fig 6.

![Figure 6 In vitro drug release studies of optimized formulation F4](image)

For optimized formulation Zero order, first order, Higuchi, Krosmeyer, Peppa’s and Hixon-crowell plots were drawn to show the mechanism of drug release from best fit $R^2$ value.

The percentage drug release was compared for F4, F7 and F14 with drug concentration from 4:2.5:1 at 1600 rpm. Percent drug release was more than 90%, but the polymer with lower concentration of polymer released the drug faster than the formulation with higher concentration of polymer. Time taken for drug release was found to be 8 h, 10 h and 12 h for F14, F7 and F4 respectively. Here the drug release was maximum for intended period of time with F4 formulation, so it is considered to be the best. Release of drug by is diffusion process. A “$n = 0.2$” for Peppas equation show that the release was Fickian release.

CONCLUSION

Effect of various independent variables on percent drug entrapment and particle size was studied by using factorial design to obtained optimized formulation. From the result it can be concluded that these variables had significant effect on the responses. Ethyl cellulose can be used to formulate an efficient floating multiparticulate system of metoprol tartrate with good percentage entrapment efficiency and particle size. Particle size analysis revealed that particles were of the size range of 56-186 µm, with porous nature and good flow properties thus exhibiting excellent buoyancies in simulated gastric fluid. In vitro drug release studies showed that release from the microsphere get successfully retarded for over 12 h. This multiparticulated delivery system can prove to be a better option as compared to other oral dosage forms.

Conflict of interest: Authors have declared that there is no conflict of interest.

Compliance with ethical standards: This manuscript does not contain any studies with human or animal subjects conducted by any of the authors.

References


