Design and Optimization of Bilayer Floating Gastroretentive Tablets of Metoprolol

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Abstract

Objectives: We aimed to formulate and optimize bilayer tablets of metoprolol tartrate consisting of both immediate and sustained release layer.

Methods: A $2^3$ factorial design was employed in formulating the GFDDS in which parameters, such as amount of HPMC ($X_1$), sodium bicarbonate + citric acid ($X_2$), and crospovidone ($X_3$) were characterized as independent variables, whereas percent metoprolol release at 30 min ($Y_1$), 4 hr ($Y_2$), 8 hr ($Y_3$), floating lag time ($Y_4$), and total floating time ($Y_5$) were considered as dependent variables. Findings: The formulations showed the biphasic release of metoprolol, where the immediate layer was completely disintegrated within 30 min and the release of the sustained layer was extended to 8 hr. Prompt disintegration of the immediate layer was facilitated by the combined effects of sodium starch glycolate and sodium bicarbonate + citric acid, whereas the extended release was assisted by HPMC. Formulations, where HPMC played the major role, were considered the best formulations. A good correlation was displayed between the experimental and predicted values that confirm the practicability of the model.

Application/improvements: This study shows the effect of various variables in the release of metoprolol tartrate and formulates the bilayer tablets of metoprolol tartrate for the immediate and sustained drug release.

Keywords: Metoprolol, Floating Drug Delivery System, Bilayer, Immediate Release Layer, Sustained Release Layer

1. Introduction

Among the various routes of drug administration, the oral route of drug administration has gained wide acceptance for decades. Oral route of drugs has been the most popular route of drug administration because of ease of administration, avoidance of pain, higher dosage accuracies, better patient compliance, cost-effectiveness, and formulation flexibilities. Moreover, to control the spatial and temporal delivery of drugs, various release-modified formulations, such as controlled release drug delivery system (CDDS) and sustained release drug delivery systems (SDDS) were developed. The release-modified dosage forms have various advantages over conventional dosage forms, such as better control of drug plasma concentration through a typical pattern, maintaining the sufficient drug concentration in plasma for longer and efficient therapeutic effect, reduction in frequency of dosing, and removal of unwanted side effects due to fluctuating plasma drug level. These advantages of modified release dosage forms have immensely increased their popularity over conventional oral dosage.

Although several conventional pharmaceutical products for oral delivery have been designed for decades, multiple drug dosing, lesser patient compliance, and lesser effectiveness of drugs have made modified release formulations more popular. While sustained release formulation of drugs assist in maintaining the drug plasma concentration for a longer period, an immediate effect of the drug is still desirable, particularly in life-threatening conditions, such as heart diseases. Therefore, with the aim to develop a formulation that would help to

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reach the blood drug therapeutic level in few minutes of drug administration and maintain a steady-state plasma concentration for a long period, a bilayer tablet model was designed that comprise both immediate release and sustained release layers of metoprolol. Moreover, to avoid the rapid efflux movement of the gastrointestinal tract, and to improve the solubility and bioavailability of the drug, the gastro-retentive system was designed. Various attempts, such as floating dosage form, mucoadhesive system, high-density system, modified shape system, gastric-emptying delaying device system and co-administration of gastric-emptying delaying drugs have been investigated to retain the dosage form in the stomach and increase the retention time. Among the aforementioned ways of gastric retention, the floating dosage form has been a commonly used system. The bulk density of the system would be lesser than the gastric fluid and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period releasing the drug at a slow and steady rate. After the release of the drug, the residual system would be emptied into the intestine. The consequence of the system would be the better control of the fluctuations in plasma drug concentration.

Metoprolol is a beta-adrenergic receptor blocking agent, popularly known for the management of hypertension. It is extensively metabolized in liver, primarily by CYP2D6, with the half-life of 3–4 hr. Since the half-life of the drug is very less, multiple doses of the drugs would be needed to maintain a constant plasma concentration for a good therapeutic response. Therefore, in the present study, to improve the limitations of conventional dosage forms, a bilayer drug model of metoprolol was designed in which one layer would provide the rapid burst of metoprolol for the immediate effect and the sustained layer would provide the extended-release of metoprolol to maintain the steady-state plasma concentration for a period.

2. Materials and Methods

2.1. Materials

Metoprolol tartrate was purchased from Shreeji Pharma International, Gujarat, India. Tartrazine, hydroxypropyl methylcellulose (HPMC K-100) and magnesium stearate were purchased from Central Drug House Pvt. Ltd., New Delhi, India. Sodium bicarbonate (SBC) was purchased from Ranbaxy Laboratories Ltd, New Delhi, India. Citric acid was purchased from Glaxo Smith Kline Pharmaceuticals Ltd, Mumbai, India. PVP K-30 and crospovidone (CP) were purchased from BASF Corporation, India. Talc was purchased from Nikita Pharmaceuticals, India. Dibasic calcium phosphate dihydrate (DCP) was purchased from Qualigens Fine Chemicals, India and SSG were purchased from and Amishi Drugs and Chemicals, India.

2.2. Pre-formulation Studies

For pre-formulation characterizations, tests such as bulk density, tapped density, Hausner’s ratio, and compressibility index were measured for metoprolol according to the established methods.

2.3. Experimental Design

A 2-level 3-factors full-factorial design consisting of eight design points was designed and experimented. The composition of the immediate layer and sustained layer is shown in Tables 1 and 2 respectively. These designs were tested against 3 independent and 5 dependent variables. The three independent variables were the concentration of HPMC (X1), SBC & citric acid in a ratio of 1:0.76 (X2), and concentration of CP (X3). Moreover, 5 dependent variables were percent release of metoprolol in 30 min (Y1), percent release of metoprolol in 4 hr (Y2), percent release of metoprolol in 8 hr (Y3), floating lag time (Y4) and total floating time (Y5). Each dependent and independent variables were investigated in relation to the drug release profiles of immediate and sustained release layers.

2.4. Formulation of Immediate and Sustained-release Layer

For formulating the immediate release layer, various ingredients were mixed together to prepare A_mix, B_mix, and C_mix. A_mix comprises of metoprolol and DCP, B_mix comprises of PVP K-30 and SSG and C_mix comprises of magnesium stearate, talc, and tartrazine. A_mix and B_mix were mixed together by doubling up technique and finally, C_mix was added into the final mixture of A_mix and B_mix and mixed adequately. Similarly, for the sustained release layer, various ingredients were mixed together to prepare A_mix, B_mix, and C_mix. A_mix comprises of metoprolol, DCP, HPMC 100,000 cps, and CP, B_mix comprise of PVP K-30 and SBC and C_mix comprise of...
magnesium stearate, talc, and citric acid. $A_{\text{mix}}$ and $B_{\text{mix}}$ were mixed together by doubling up technique and finally, $C_{\text{mix}}$ was added into the final mixture of $A_{\text{mix}}$ and $B_{\text{mix}}$ and mixed adequately.

### 2.5. Tablet Formulation

Eight batches of bi-layered tablets were prepared that contained 70 mg of metoprolol. Eight-millimeter round, biconvex tablets were compressed in a 10-station rotary compression machine. The required amount for the individual tablet was weighed separately, 100 mg for the immediate-release layer and 270 mg for the sustained-release layer. The first ingredients mix of the immediate layer was poured into the die, its level was maintained by tapping the punches up and down and then the ingredient mix of sustained-release layer was poured and tablets were compressed. The hardness and diameter of all tablets were maintained according to the monographs of Indian pharmacopeia standard.\(^{19}\)

### 2.6. Development and Constituents of Immediate and Sustained Release Layer

The immediate layer consisted of fixed ratio of metoprolol, 20%; SSG, 15%; PVP K-30, 5%; magnesium stearate, 1%; talc, 1.40%; DCP, 46.94%; SBC, 6%; citric acid, 4.56%; and tartrazine, 0.10% of 100 mg. Similarly, sustained release layer consisted of metoprolol, 18.51%; PVP K-30, 5%; magnesium stearate, 1%; talc, 1%; HPMC, 14%-25%; CP, 3-6%; DCP, 29.84%-43.36%; SBC, 3.77%-7.77%; Citric acid, 4.56%-6.08% of 270 mg.

### 2.7. Evaluation of the Tablets

Various *in vitro* tests, such as weight variation, thickness variation, diameter variation, hardness, friability, disintegration, and dissolution studies were conducted for each of the formulations according to the pharmacopoeia method.\(^{19}\) Calibration curves were prepared by plotting concentration vs absorbance reading at UV-wavelength of 274 nm for different concentrations of metoprolol ranging from 10-250 µg/ml. Dissolution studies of tablets were carried out in a dissolution medium of 0.1N HCl (750 ml; pH 1.2) with tablet dissolution tester, USP type I. The study was carried out at a speed of 100 rpm for 8 hr at a temperature of 37 ± 0.5°C. Dissolution samples at various time intervals of 10 min, 30 min, 1 hr, 4 hr, and 8 hr were withdrawn from the dissolution basket, filtered, and analyzed by UV-spectrophotometer at 274 nm. The drug release amounts were calculated using the standard calibration curve.

### 3. Results and Discussion

#### 3.1. Physicochemical Parameters

Different physicochemical parameters of the formulated products such as shape, color, size, hardness, weight variation, and assay were assessed according to the Indian pharmacopoeia standards.\(^{19}\) Considering the eight formulated products, all the formulated products were within the pharmacopoeial requirements of ± 5% of weight variation, 6.28 ± 0.1113 mm for thickness, and 8.14 ± 0.046 mm for diameter. The hardness of the formulated products measured by Schleuniger automatic hardness tester was maintained within 40.09 ± 28.96 kg/

### Table 1. Composition of immediate release layer

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<th>F5</th>
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cm$^2$. The assay values of the formulations were observed to be between 98.5%–109.1%.

3.2. Dissolution Studies of Formulated Products

Release profiles of eight formulations with $2^3$ factorial designs are shown in Figures 1A and B. Various factors, such as the concentration of HPMC, CP, and SBC & citric acid in a fixed ratio of 1:0.76 were considered to have an optimal effect on the release profile of metoprolol. The formulations showed the biphasic release of metoprolol. The first layer, the immediate release layer of the drug was released in less than 30 min and the second layer, the sustained release layer of metoprolol was released up to 8 hr. The prompt disintegration of the fast releasing layer was facilitated by SSG and SBC combined with citric acid in a fixed ratio. However, the release of the sustained release layer was dependent upon the factors, such as the concentration of HPMC, SBC, and CP. Among eight formulations, F$_4$ and F$_8$ were observed to have different release profiles of metoprolol when compared to other formulations (Figures 1A and B). The results obtained from the experiments were statistically analyzed for response variables by using Statgraphics, version-15, and factorial linear interactive first-order model.

3.3. Effect of Formulation Variables on Response Variables $Y_1$, $Y_2$, and $Y_3$

In the case of $Y_1$ (% metoprolol released at 30 min), none of the independent variables, such as $X_1$, $X_2$, $X_3$; $X_1 X_2$; $X_1 X_3$; and $X_2 X_3$ showed any significant effect on the release of metoprolol in 30 min as shown in Pareto chart (Figure 2A). However, according to the main effect plot for 30 min, with the increase in the concentration of HPMC from 40.5 to 67.5 mg/tablet, the release rate was dramatically inhibited. However, CP had shown the opposite effects on the release of metoprolol at 30 min, as shown in Figure 2B. When the concentration of CP increased from 8.1 to 15 mg/tablet, the release rate of metoprolol was increased. Although the release of metoprolol was dependent on the concentration of SBC, the effect was not profound. The relationship between variables was further elucidated using Contour plot analysis. The effect of $X_1$ and $X_2$ on $Y_1$ at a fixed concentration of $X_3$ (11.55) was shown in Figure 1C. When $X_1$ increased from $-1$ level to $+1$ level, $Y_2$ decreased from 75 to 53% when the total HPMC concentration ($X_1$) was increased and SBC concentration ($X_2$) was kept at the highest level.

The percentage of metoprolol released at 4 hr was similar to the release profile at 30 min. In case of $Y_2$ (% metoprolol released at 4 hr), none of the variables ($X_1$, $X_2$, $X_3$; $X_1 X_2$; $X_1 X_3$; and $X_2$, $X_3$) had significant effects on the release rate of metoprolol at 4 hr as shown in Pareto Chart (Figure 2D). As per the main effect plot of 4 hr (Figure 2E), the concentration of HPMC had shown to have a direct effect on the release of metoprolol. Moreover, when the concentration of HPMC was increased from 40.5 to 67.5, the release of metoprolol was drastically reduced. In contrast, the release rate was increased when the concentration of CP was increased from 8.1 to 15%.

However, the change in concentration of SBC had very little effect on the release profile of the metoprolol (Figure 2E). The relationship between variables was further elucidated using Contour plot analysis (Figure 2F). The effect of $X_1$
and $X_2$ on $Y_2$ at fixed concentration of $X_3$ (11.55) were determined. When $X_1$ increased from the $-1$ level to the $+1$ level, $Y_2$ decreased from 76 to 92.5% when the total HPMC concentration ($X_1$) was increased and the SBC concentration ($X_2$) was kept at the highest level.

The percentage of metoprolol released at 8 hr ($Y_3$) was different from the release profile at 30 min and 4 hr. The $X_1$ (HPMC) variable had significant effect on decreasing the release rate of metoprolol at 8 hr, whereas other variables ($X_2$, $X_3$, $X_1$, $X_2$, $X_1$, $X_3$, and $X_2$, $X_3$) did not show any significant effects on the release rate of metoprolol at 8 hr as shown in Pareto Chart (Figure 2G). Lesser the HPMC and higher the CP concentrations, more positive the effects on the release profile of metoprolol was observed, as shown in Figure 2H. With the increase in HPMC from 40.5 to 67.5 mg/tablet, the release rate of metoprolol was decreased. However, the release rate was increased when the concentration of CP increased from 8.1 to 15 mg/tablet. On the other hand, the concentration of SBC did not have any effect in the release of metoprolol as shown in Figure 2H. The relationship between variables was further elucidated using the Contour plot (Figure 2I). The effects of $X_1$ and $X_2$ on $Y_2$ at a fixed level of $X_3$ (11.55) was presented. When $X_1$ was increased from the $-1$ level to the $+1$ level, $Y_5$ (% metoprolol released at 8 hr) decreased from 102.5 to 86%. The total HPMC concentration ($X_1$) was increased from 40 mg to 70 mg/tablet and the SBC concentration ($X_2$) was kept at the highest level. The possible reason for the better-extended release profile of formulations would be explained by the mechanism by which HPMC impedes drug release. It has the ability to form a gel layer at the matrix periphery exposed to the aqueous fluid. The drug would release from the matrix mainly by diffusion through water-filled pores. Consequently, the release rate is associated with porosity and tortuosity of the pores and the swellable matrix is primarily attributed to polymer swellability. Therefore, the increase in proportions of HPMC in the matrix would decrease the release rate of the drug. The extended release formulations prepared using HPMC would form three fronts during the dissolution process such as the swelling front (polymer glassy-rubber

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**Figure 2.** Analysis of factors that affects the release of metoprolol. (A), (D) and (G) standardized Pareto chart for 30 min, 4 hr and 8 hr, respectively. (B), (E), (H) main effect plot for 30 min, 4 hr and 8 hr, respectively. (C), (F), (I) counter plot for 30 min, 4 hr and 8 hr, respectively.
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The distance between the erosion front and swelling fronts forms the gel layer and that of diffusion front and the erosion front represented the dissolved drug gel layer, which is the diffusive layer involved in controlling the drug's release profile.23 The gel layer formed on the surface of the tablet is relatively thicker when a higher concentration of HPMC is used.23 Although, the higher concentration of HPMC had the inhibitory effect in the release rate of metoprolol, comparing the dissolution profiles of eight formulations (F1 to F8), the release of drug was found to be appreciable in case of F4 and F8 using HPMC of concentration, 67.5 mg/tablet, which showed better-extended release profile. However, in formulations, such as F6 that contained the low HPMC concentration, the release rate of metoprolol was not prolonged. This might be because of the poor matrix strength of HMPC.25 Similarly, in the formulations, such as F1, F2, F3, and F7, the drug release from the system was at a higher rate due to the high concentration of CP or SBC + citric acid in a fixed ratio of 1:0.76 or both. When the tablets encounter the dissolution medium (0.1 N HCl), CO2 gas was generated from tablets with the reaction of SBC and citric acid.26 This phenomenon could form pores after CO2 liberated from the tablets, which further facilitated the permeation of solvent into the system.26 This process contributes swelling of polymer and dissolution of drug molecules. The dissolved drug molecules will have a relatively easier escape from such pores (channels) leading to higher drug release.26

3.4. Analysis of Formulation Variables on Floating Lag Time (Y4)

In the case of Y4 (floating lag time), none of the variables (X1, X2, X3; X1, X2; X1, X3 and X2, X3) showed any significant effect on floating lag time as shown in Pareto Chart (Figure 3A). When the concentration of HPMC and SBC was increased from 40.5 to 67.5 mg/tablet and 16.2 to 21.6 mg/tablet, respectively, the floating lag time decreased drastically. In contrast, when the concentration of CP increased from 8.1 to 15 mg/tablet, a proportional increase in floating lag time was noticed. Furthermore, the effect of HPMC, CP + SBC (11.55) on the floating lag time was elucidated by Contour plots (Figure 3C). As shown in the figure, when X1 increased from the −1 to +1 level, Y4 decreased from 880 seconds to 0 seconds when the total HPMC concentration (X1) was increased and the SBC concentration (X2) was kept at the highest level. For all the formulations, the time required for the tablets to move from bottom to top of a beaker containing pH 1.2 at 37°C ± 1°C was less than 30 min.

3.5. Analysis of Formulation Variables on Total Floating Time (Y5)

The variable X1 was found to have significant positive effects on increasing Y5 (total floating time) while other

![Figure 3](image-url). Floating lag time and total floating time of formulations. (A) and (D) standardized Pareto chart for floating lag time and total floating time, respectively. (B) and (E) main effect plot for floating lag time and total floating time, respectively. (C) and (F) counter plot for floating lag time and total floating time, respectively.
variables ($X_2$, $X_3$; $X_1$, $X_2$; $X_1$, $X_3$, and $X_2$, $X_3$) did not have any significant effect on total floating time as shown in Pareto Chart (Figure 3D). When the concentration of HPMC increased from 40.5 to 67.5 mg/tablet, a significant increase in total floating time was observed. However, when the concentration of SBC was increased from 16.2 to 21.6 mg/tablet, a slight decrease in total floating time was noticed (Figure 3E). Likewise, when the concentration of CP was increased from 8.1 to 15, no significant change in total floating time was noted (Figure 3E). Once the tablets floated to the surface, they remained buoyant for up to 8 hr, during which the tablets lost their integrity and the size of the swollen matrix gel drastically reduced because of disintegration and erosion. In fact, the floating time (buoynancy) of the tablets would be governed by two mechanisms. First, when the tablets encounter the gastric fluid, swelling (hydration) of the hydrocolloid particles occurs on the tablet's surface which in turn results in an increase in bulk volume. Second, the presence of the internal voids (porosity) in the tablets helps to float the formulation in the simulated gastric solution. When these two factors come into effect, the tablets acquire a bulk density of less than one and remain buoyant on the gastric fluid.

### 3.6. Optimization for the Best Formulation

The process was optimized for the response $Y_1$ to $Y_5$, and the optimized formulation was achieved by minimizing the floating lag time, maximizing the total floating time and the percentage of metoprolol release at 8 hr. The results from the optimization clarified the optimum settings for the bilayer floating tablets with a high total polymer HPMC, SBC, and low total polymer concentration of CP. To verify the reproducibility, a new formulation (the composition of the optimized formulations as shown in Table 3) was prepared according to the predicted levels and observed level of ingredients (Table 4). According to the $F_1F_2$ test, the similarity factor $F_2$ between the experimental and predicted values were observed to be 88 as shown in Table 5.

The experimental values for floating lag time and total floating time were 85.34 sec and 7.81 hr and predicted values were 192 sec and 8 hr, respectively. This showed a good relationship between the experimental and predicted values, which confirms the practicability of the model.

In our present investigation, an attempt was made to investigate the effect of formulation variables on FDDS for an antihypertensive drug-metoprolol. Various formulations with varying concentrations of ingredients were formulated and experimented. Among 8 formulations, $F_2$ and $F_6$ were found to be the best because they showed delayed-release, and the drug release in simulated gastric acidic buffer (0.1N HCl) was found to be almost complete in 8 hr. Moreover, an optimized formulation with optimum floating lag time, total floating time and extended-release of metoprolol were designed and analyzed. The present study showed a good correlation between the predicted and observed values for the most probable optimal formulations.

### Table 2. Composition of sustained release layer

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4. Conclusion

This study investigated the various factors, which could affect the release of drug from bilayer tablets of metoprolol tartrate. Combined effects of sodium starch glycolate, sodium bicarbonate + citric acid provide the better results for the instantaneous disintegration of the immediate release layer and HPMC played a significant role for the extended-release of the sustained release layer.

Conflict of Interests

None.


