Optimization Of Propranolol Hydrochloride Controlled Release Matrix Tablet Using Factorial Design

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Article ID: WMC00914
Article Type: Research articles
Submitted on: 06-Oct-2010, 08:12:05 AM GMT   Published on: 06-Oct-2010, 07:29:58 PM GMT
Article URL: http://www.webmedcentral.com/article_view/914
Subject Categories: PHARMACEUTICAL SCIENCES
Keywords: Propranolol Hydrochloride, Hydroxypropylmethylcellulose K15M, Carbopol 934P, Controlled release, Matrix tablet

How to cite the article: Patel R, Patel H, Patel G. Optimization Of Propranolol Hydrochloride Controlled Release Matrix Tablet Using Factorial Design. WebmedCentral PHARMACEUTICAL SCIENCES 2010;1(10):WMC00914
Optimization Of Propranolol Hydrochloride Controlled Release Matrix Tablet Using Factorial Design

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Abstract

Purpose: The objective of this study was to prepare Propranolol Hydrochloride controlled release matrix tablets and to investigate the effect of the polymer blends and the polymer concentration on drug release.

Method: Propranolol Hydrochloride controlled release matrix tablets were prepared by direct compression technique. Hydroxypropylmethylcellulose K15M (HPMC K15M) and Carbopol 934P were used in formulating the matrix tablets. A 32 full factorial design were applied to carry out systematic studies. The blending ratio of HPMC K15M and Carbopol 934P (X1) and Polymer concentrations (X2) were selected as independent variables. The time required for 50% (t50) and 80% (t80) drug release were selected as dependent variables. The dissolution profile of all the batches was fitted to zero-order, first-order, Higuchi, and Korsemeyer and Peppas models to ascertain the kinetic modeling of drug release.

Results: The results clearly indicate that the values of t50, t80, f2 and MDT are strongly dependent on the independent variables. In-vitro drug release profile of all possible batches of factorial design was compared with theoretical drug release profile. The results indicate that batch F7 showed the highest value among all the batches, and it also shows similarity in t50 and t80 values. The f2 value (74) of batch F7 indicates less than 5% difference in in-vitro drug release profile with theoretical release profile.

Conclusions: It was observed that the blending ratio of HPMC K15M-Carbopol 934P and polymer concentration have distinct effect on in-vitro drug release profile. Release rate of Propranolol hydrochloride decreased proportionally with increased in concentration of Carbopol 934P and total polymer concentration.

Introduction

Propranolol hydrochloride is an b-adrenergic blocker and it has been widely use for the treatment of hypertension and angina. Propranolol hydrochloride is highly lipophilic and is almost completely absorbed after oral administration. Its oral bioavailability is about 26±10% and t½ is about 3.4±1.3 hour.1 The objective of present work was to optimize the formulation of Propranolol hydrochloride controlled release matrix tablet containing Hydroxypropyl-methylcellulose K15M and Carbopol 934P using 32 full factorial design. Use of a hydrophilic polymer matrix system is one of the most popular approaches in formulating a controlled release dosage form.2,3,4 There are few reports on the application of Carbopol with HPMC for controlled release matrix tablets.5,6,7,8,9 In the present work, it was intended to study the effect of polymer blend and polymer concentration on the in-vitro drug release rate from matrix tablets using full factorial design. The factorial design was used, selecting two independent variables X1 as blending ratio of HPMC K15M and Carbopol 934P and X2 as polymer concentration. The time necessary for the in vitro release of 50% (t50) and 80% (t80) of the drug dose was selected as the response variables. Response surface and grid plot were performed from statistical mathematical models. Similarity factor (f2) and Mean dissolution time (MDT) values calculated from the data. The in vitro release data obtained were fitted in to various kinetic models (zero order, first order and Higuchi Equation). And to find out release mechanism the in vitro release data were applied in Korsmeyer–Peppas equation.

Methods

Preparation of Propranolol Hydrochloride matrix tablet
Propranolol Hydrochloride controlled release matrix tablets were prepared by direct compression technique, according to the formulation. For each formulation, the drug and polymer(s) were weighed and premixed for 5min. Filler and glidant were added and mixed for 10min. Magnesium stearate was added at the end and mixed for additional 2min. The formulations were compressed on an automated rotary press using 9.6mm round-concave punch to 300mg target tablet weight and 4-6kg/cm2 tablet hardness.
In-vitro drug release studies
In-vitro drug release was tested according to USP 24 NF 19 modified release products in apparatus 1 at 50 rpm, using 750 ml of 0.1N HCl for the first two hours followed by 1000 ml of pH 6.8 buffer (adjusted by addition of 250 ml of 0.2 M trisodium phosphate). 10 ml sample was withdrawn at appropriate time interval and replaced fresh dissolution medium. The samples were analyzed at 288 nm using reference blank dissolution medium on Systronic 2201 UV-VIS spectrophotometer. The drug release study was conducted in triplicate and mean values were plot.

Water uptake studies
Water uptake study was carried out by putting tablet into petridish containing 0.1N HCl for the 2 hour followed in pH 6.8 buffer solution up to 12 hour at 37±1°C. At predetermined time intervals (2, 4, 6, 9, and 12 hour), tablets were removed from the medium and lightly blotted using tissue paper and weighed. The following equations were used to determine percent weight gain (water uptake).12

Full Factorial Design
A 32 full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The blending ratio of HPMC K15M and Carbopol 934P (X1) and Polymer concentrations (X2) were selected as independent variables. The times required for 50% (t50) and 80% (t80) drug dissolution were selected as dependent variables.

Comparison of in-vitro release profile
The in-vitro drug release profile of all batches with theoretical drug release profile was compared using similarity factor (f2), given by Scale Up and Pose Approval Changes (SUPAC) guidelines for modified release dosage form. 11

Mean dissolution time (MDT) of all batches were calculated using equation reported by Paulo Costa, 2001.11

Kinetic modeling and mechanism of drug release
The dissolution profile of all the batches was fitted to zero-order, first-order, Higuchi, and Korsemeyer and Peppas models to ascertain the kinetic modeling of drug release according the method reported by Paulo Costa, 2001.11

Results and Discussion
An ideal controlled release tablet should release the required quantity of drug with predetermined kinetics in order to maintain effective drug plasma concentration. To achieve constant drug plasma concentration, tablet should be formulated in such a way that it can release the drug in a predetermined and reproducible manner.

Optimization of tablet formulation using 32 full factorial design
A 32 full factorial design was constructed to study the effect of the blending ratio of HPMC K15M and Carbopol 934P (X1) and the Polymer concentration (X2) on the drug release from controlled release matrix tablets. The time required for 50% and 80% drug release were selected as dependent variables.

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response. where Y is the dependent variable, b0 is the arithmetic mean response of the 9 runs, and bi is the estimated coefficient for the factor Xi. The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1 X2) show how the response changes when 2 factors are changed simultaneously. The polynomial terms (X12 and X22) are included to investigate nonlinearity.

The full Equation (equation containing only statistically significant terms) is then used for drawing counter plots to visualize the impact of changing variables at a glance. The optimum point may be identified from the plot.

The formulations and results of in-vitro drug release study of factorial batches (F1 to F9) are shown in Table 1.

The statistical analysis of the factorial design batches was performed by multiple linear regression analysis carried out in Microsoft Excel. The t50, t80, f2 and MDT values for the 9 batches (F1 to F9) showed a wide variation; the results are shown in Table 1. The data clearly indicate that the values of t50, t80, f2 and MDT are strongly dependent on the independent variables. The fitted Equations relating the response t50, t80, f2 and MDT to the transformed factor are shown in following Equations

\( r^2 = 0.9934 \)

\( r^2 = 0.98724 \)

The values of the correlation coefficient indicate a good fit. The polynomial Equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, (i.e. positive or negative).

The response surface plot and counter plot were drawn using Sigma Plot Software 10.0 version. The data demonstrate that both X1 and X2 affect the in-vitro drug release (t50 and t80). The shaded area in the Figure 2 (±5% level from theoretical value) demonstrated the optimize area for both dependent...
variable (t50 and t80).

It may also conclude that the X1 (blending ratio of HPMC K15M and Carbopol 934P) and X2 (polymer concentration) appear to favor the preparation of Propranolol hydrochloride controlled release tablets. It can conclude that the drug release profile may be changed by appropriate selection of the X1 and X2 levels. The shaded area (X1 and X2) in counter plot (Figure 2) will give nearly theoretical desired release profile of Propranolol hydrochloride controlled release matrix tablet.

**Comparison of in-vitro drug release profile**

The similarity factor (f2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profiles.13 The dissolution profiles are considered to be similar when f2 is between 50 and 100.

In-vitro drug release profile of all possible batches of factorial design was compared with theoretical drug release profile. The results in Table 1 indicate that batches F1, F2, F3, F4, F5, F6 and F7 fulfill the above criteria. But batch F7 showed the highest value among all the batches, and this similarity is also in t50 and t80 values. The f2 value (74) of batch F7 indicates less than 5% difference in in-vitro drug release profile with theoretical release profile. The similarity between the theoretical release profile and the in-vitro drug release profile of F7 is clearly demonstrated in Figure 3.

In-vitro release study of marketed formulation of Propranolol hydrochloride

In-vitro drug release studies of Propranolol hydrochloride marketed formulations (M1- extended release, M2- time release, and M3- sustained release) were carried out using experimental condition as described above. Figure 4 shows the in-vitro drug release profile of marketed formulations and comparison with theoretical drug release profile.

Further to evaluate complete similarity of optimize region in Figure 1, F10 batch was prepared with X1: + 0.75 (coded value) for blending ratio of HPMC K15M and Carbopol 934P and X2: -1 (coded value) for polymers concentration. In-vitro drug release was performed according to procedure. The results in Table 2 also indicated a similarity between F10 and Theoretical drug release profile.

**Water uptake studies**

Water uptake of Propranolol hydrochloride controlled release tablet was significantly greater in high concentration of HPMC K15M containing formulation (Figure 5). Marcos et al studies the potential of combining Carbopol 974P and HPMC K4M using Propranolol hydrochloride as a model drug and found that the amount of water imibed in Carbopol was lower than that by HPMC alone or 1:1 mixture of two polymers. 5 So, as concentration of Carbopol 934P increases the water uptake of tablets was lower.

**Kinetic Modeling and Mechanism of drug release**

The in-vitro release data obtained were fitted in to various kinetic Equations. Correlations of individual batch with applied Equation are given in Table 3. The release rates were calculated from the slope of the appropriate plots.

To find out release mechanism the in-vitro release data were fitted in Korsmeyer-Peppas equation where n is a factor, which indicates the mechanism of the drug release. For instance n: 0.5 for square root of time (pure diffusion controlled drug release) and n: 1 for zero order release. The values of n >1.0 indicates anomalous diffusion (swelling-controlled drug release or Case II transport) for all selected formulations. The release exponent n was determined and given in Table 3. All batches showed higher correlation with Highchi plot than zero order and first order. Batch F7 showed diffusion controlled release where as other batches shows anomalous effect (combined mechanism of diffusion and case II transport).

**Conclusion(s)**

It was observed that the blending ratio of HPMC K15M-Carbopol 934P and polymer concentration have distinct effect on in-vitro drug release profile. Use of Carbopol 934P and HPMC K15M (hydrophilic polymer) is an advantageous combination for formulating matrix tablets for direct compression. Release rate of Propranolol hydrochloride decreased proportionally with increased in concentration of Carbopol 934P and total polymer concentration. The results of full factorial design was indicated that the X1 (the blending ratio of HPMC K15M and Carbopol 934P) and X2 (polymer concentration) both have significant effect on in-vitro drug release profile. No significant difference was observed between desired release profile and batch F1, F2, F3, F4, F5, F7 and F8. Batch F7 showed highest f2 (74) among all the batches. With marketed formulation M3 showed highest f2 (83.55) among all batches. To evaluate optimize region in counter plot F10 batch was prepared. From in-vitro drug release profile of batch F10 showed f2 (67), this indicate similarity with desired release profile.

**References**

Illustrations

Illustration 1

Formulation and in-vitro drug release characteristics of batches in 3^2 Full Factorial Design

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Variable level in coded form</th>
<th>t50 (min)</th>
<th>t80 (min)</th>
<th>Similarity factor ($f_2$)</th>
<th>MDT (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>-1 -1</td>
<td>184</td>
<td>461</td>
<td>53.52</td>
<td>230</td>
</tr>
<tr>
<td>F2</td>
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<td>274</td>
<td>545</td>
<td>69.23</td>
<td>298</td>
</tr>
<tr>
<td>F3</td>
<td>-1 +1</td>
<td>314</td>
<td>596</td>
<td>53.77</td>
<td>332</td>
</tr>
<tr>
<td>F4</td>
<td>0 -1</td>
<td>205</td>
<td>489</td>
<td>62.85</td>
<td>249</td>
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<tr>
<td>F5</td>
<td>0 0</td>
<td>292</td>
<td>581</td>
<td>60.18</td>
<td>317</td>
</tr>
<tr>
<td>F6</td>
<td>0 +1</td>
<td>337</td>
<td>642</td>
<td>47.99</td>
<td>353</td>
</tr>
<tr>
<td>F7</td>
<td>+1 -1</td>
<td>244</td>
<td>555</td>
<td>73.85</td>
<td>289</td>
</tr>
<tr>
<td>F8</td>
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<td>320</td>
<td>603</td>
<td>52.41</td>
<td>337</td>
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<tr>
<td>F9</td>
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<td>701</td>
<td>39.35</td>
<td>392</td>
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<tr>
<td>Theoretical</td>
<td>--- ---</td>
<td>236</td>
<td>526.5</td>
<td>---</td>
<td>275.5</td>
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</table>

<table>
<thead>
<tr>
<th>Coded Values</th>
<th>Actual Values</th>
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<tbody>
<tr>
<td>X1</td>
<td>X2</td>
</tr>
<tr>
<td>-1</td>
<td>0.7:0.3</td>
</tr>
<tr>
<td>0</td>
<td>0.5:0.5</td>
</tr>
<tr>
<td>+1</td>
<td>0.3:0.7</td>
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</tbody>
</table>
Illustration 2

Comparison of check points between F10, Marketed formulations and theoretical drug release profile

<table>
<thead>
<tr>
<th>Check points</th>
<th>Theoretical Profile</th>
<th>Calculated valued from Equation</th>
<th>F10</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{50}$ (min)</td>
<td>236</td>
<td>229.5</td>
<td>224</td>
<td>513</td>
<td>771</td>
<td>239</td>
</tr>
<tr>
<td>$t_{80}$ (min)</td>
<td>526</td>
<td>531</td>
<td>518</td>
<td>913</td>
<td>1529</td>
<td>543</td>
</tr>
<tr>
<td>$F_2$</td>
<td>---</td>
<td>69</td>
<td>67</td>
<td>28.56</td>
<td>23.6</td>
<td>83.55</td>
</tr>
<tr>
<td>MDT (min)</td>
<td>275.5</td>
<td>275</td>
<td>258</td>
<td>464.4</td>
<td>498.8</td>
<td>282.6</td>
</tr>
</tbody>
</table>
Illustration 3

Correlation coefficient, in-vitro release rate and the release exponent of Propranolol hydrochloride

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
<th>Korsmeyer-Peppas</th>
<th>Release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>$k_0$ (h$^{-1}$)</td>
<td>$r^2$</td>
<td>$K_1$ (h$^{-1}$)</td>
<td>$r^2$</td>
</tr>
<tr>
<td>F1</td>
<td>0.9099</td>
<td>7.49</td>
<td>0.9275</td>
<td>0.3422</td>
<td>0.9929</td>
</tr>
<tr>
<td>F2</td>
<td>0.9661</td>
<td>7.27</td>
<td>0.9273</td>
<td>0.2266</td>
<td>0.9888</td>
</tr>
<tr>
<td>F3</td>
<td>0.9683</td>
<td>6.95</td>
<td>0.9777</td>
<td>0.172</td>
<td>0.9864</td>
</tr>
<tr>
<td>F4</td>
<td>0.9251</td>
<td>7.27</td>
<td>0.9083</td>
<td>0.287</td>
<td>0.9974</td>
</tr>
<tr>
<td>F5</td>
<td>0.9614</td>
<td>6.88</td>
<td>0.976</td>
<td>0.1801</td>
<td>0.9896</td>
</tr>
<tr>
<td>F6</td>
<td>0.969</td>
<td>6.46</td>
<td>0.9853</td>
<td>0.1453</td>
<td>0.9868</td>
</tr>
<tr>
<td>F7</td>
<td>0.9348</td>
<td>6.67</td>
<td>0.8949</td>
<td>0.2063</td>
<td>0.9961</td>
</tr>
<tr>
<td>F8</td>
<td>0.977</td>
<td>6.9</td>
<td>0.9817</td>
<td>0.167</td>
<td>0.9861</td>
</tr>
<tr>
<td>F9</td>
<td>0.9813</td>
<td>6.23</td>
<td>0.9828</td>
<td>0.1251</td>
<td>0.987</td>
</tr>
</tbody>
</table>
Illustration 4

Response surface plot of $t_{50}$

Figure 1: Response surface plot of $t_{50}$
Illustration 5

Overlapping Counter plots of the polymer viscosity (X1) and polymer concentration (X2) verses t50 an
Illustration 6

Comparison of F7 batch with Theoretical drug release profile

Figure 3: Comparison of F7 batch with Theoretical drug release profile
Illustration 7

In-vitro drug release profile of marketed formulations

Figure 4: In-vitro drug release profile of marketed formulations.
Illustration 8

Water uptake study of Propranolol hydrochloride controlled release matrix tablets (F1-F9 batches)

Figure 5: Water uptake study of Propranolol hydrochloride controlled release matrix tablets (F1-F9 batches)
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