Chapter 5

Fabrication and evaluation of captopril modified release oral formulation:
5.0 Fabrication and evaluation of captopril modified release oral formulation

5.1 Introduction:

Designing of modified release drug delivery system of highly water soluble drug is a challenging task. Among the various methods available to formulate modified release formulations, solid dispersion has gained enormous attention. Captopril is a freely water soluble drug with an elimination half-life of 1.7 h after oral administration. It is usually prescribed to patients who are chronically ill. Various attempts have been made to design modified release formulations of captopril. Number of patents have been filed on sustained release captopril formulations. However, the information available on the application of solid dispersion in modified release of captopril is scanty.

Glyceryl behenate (Compritol® ATO 888), a waxy material with low fusion point, has gained wide acceptance as a novel modified release excipient. Barthelemy et al. explored the potential use of glyceryl behenate as a hot-melt coating agent to prolong the release of theophylline. Faham et al. studied the influence of Compritol® ATO 888 on chloroquine release. Mirghani et al. prepared sustained-release polymer beads containing diclofenac sodium and Compritol® ATO 888.
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Ethyl cellulose, hydrophobic inert polymer, is extensively used as a pharmaceutical excipient in a number of dosage forms.\textsuperscript{26-32} Shiakh et al. used ethyl cellulose as a matrix forming material for preparation of modified release dosage form of both water-soluble and water-insoluble drugs using the solid dispersion technique.\textsuperscript{33-34} The release kinetics from ethyl cellulose matrices chiefly depends on the porosity of the hydrophobic compact.\textsuperscript{35} Shlieout and Zessin reported that the compressibility of various grades of ethyl cellulose is good.\textsuperscript{36}

Artificial neural network (ANN) resembles the human brain in the way in which knowledge is acquired by the network from its environment through a learning process and interneuron connection strengths.\textsuperscript{37} ANN could be applied to quantify a nonlinear relationship between independent factors and pharmaceutical responses by means of iterative training of data obtained from a designed experiment.

The aim of the present research work was to prepare modified release oral formulation of captopril employing solid dispersion technique utilizing Compritol\textsuperscript{®} ATO 888 and ethyl cellulose as release retarding material without infringing the existing patents. A $3^2$ full factorial design was adopted for optimization using the ratio of captopril to Compritol\textsuperscript{®} ATO 888 and the amount of ethyl cellulose as independent variables. Eutectic mixture of camphor and menthol was used as a solvent for captopril to obtain uniform drug distribution. Captopril falls under Biopharmaceutical Classification System (BCS) class III drug with high solubility and poor permeability. The log P and clog P values of...
captopril are 0.23 and 0.88 respectively. Menthol is well known intestinal and dermal permeation enhancer and hence it may improve oral bioavailability of formulation. The results of design of experiments were compared with that obtained by artificial neural network (ANN) for evaluating the predictive power of both the methods.

5.2 Methods:

5.2.1 Preliminary studies:

Solution of captopril (175 mg/ml, 60±2°C) in a eutectic mixture consisting of equal parts of camphor and menthol was added with constant stirring to the melted Compritol® ATO 888 (70±2°C). The mixture was gradually cooled to ambient condition. The solidified mass was pulverized and passed through 20# mesh screen (850 μm opening) to obtain granules. The granules were additionally dried at 50±2°C in a tray dryer till the smell of camphor and menthol was not perceived. The granules were mixed with 1.5% w/w Cab-O-Sil M5 and evaluated for percentage drug content. The tablets containing 50 mg captopril with 9.5 kP crushing strength were prepared by compressing the granules on single station tablet press (Cadmach Machines Ltd., Ahmedabad, India). Batches C1-C4 contained 1:1, 1:2, 1:3 and 1:4 ratio of captopril to Compritol® ATO 888 respectively. The tablets were characterized for percentage friability and in vitro drug release (Figure 5.a).
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Figure 5.a Comparative in vitro drug release from batches C1-C4; C1 (○-), C2 (■-), C3 (×-) and C4 (△-)

5.2.2 Factorial design:

A $3^2$ full factorial design was used for optimization of the formulated products. The ratio of captopril to Compritol® ATO 888 ($X_1$) and ethyl cellulose ($X_2$) were selected as independent variables whereas the amount of drug released in 1 h ($Y_1$) and the time required to release 80% of the drug ($t_{80\%}$, $Y_2$) were selected as dependent variables. Table 5.a shows the composition, design layout for the optimization study and the responses. Table 5.b shows the result of analysis of variance (ANOVA). The results of in vitro drug release are displayed in Figures 5.b-5.c. In batches C5-C15, ethyl cellulose was added as extragranular fraction. Batch C16 contained physical mixture of captopril, Compritol® ATO 888 and ethyl cellulose in concentration equivalent to that of batch C14.
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Table 5.a Composition, $3^2$ full factorial design layout and observed responses

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Transformed Values</th>
<th>Real Values</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$X_1$</td>
<td>$X_2$</td>
<td>$Y_1$</td>
</tr>
<tr>
<td>C5</td>
<td>-1</td>
<td>-1</td>
<td>1:2</td>
</tr>
<tr>
<td>C6</td>
<td>0</td>
<td>-1</td>
<td>1:3</td>
</tr>
<tr>
<td>C7</td>
<td>1</td>
<td>-1</td>
<td>1:4</td>
</tr>
<tr>
<td>C8</td>
<td>-1</td>
<td>0</td>
<td>1:2</td>
</tr>
<tr>
<td>C9</td>
<td>0</td>
<td>0</td>
<td>1:3</td>
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<tr>
<td>C10</td>
<td>1</td>
<td>0</td>
<td>1:4</td>
</tr>
<tr>
<td>C11</td>
<td>-1</td>
<td>1</td>
<td>1:2</td>
</tr>
<tr>
<td>C12</td>
<td>0</td>
<td>1</td>
<td>1:3</td>
</tr>
<tr>
<td>C13</td>
<td>1</td>
<td>1</td>
<td>1:4</td>
</tr>
<tr>
<td>C14*</td>
<td>0.14</td>
<td>0.7</td>
<td>1:3.14</td>
</tr>
<tr>
<td>C15*</td>
<td>0.8</td>
<td>0.2</td>
<td>1:3.8</td>
</tr>
</tbody>
</table>

Each tablet contained 50 mg captopril. $X_1$ is the ratio of captopril to Compritol® ATO 888, $X_2$ is the amount of ethyl cellulose (mg), $Y_1$ is percentage of drug released in 1h, $Y_2$ is the time required to release 80% of drug release ($t_{80\%}$).

Batches C14 and C15 (*) are check-point batches.
Table 5.b Result of analysis of variance (ANOVA) of batches C5-C13

<table>
<thead>
<tr>
<th>Response</th>
<th>Source</th>
<th>SS</th>
<th>DF</th>
<th>MS</th>
<th>F</th>
<th>Prob&gt;F</th>
<th>Nature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y1</td>
<td>$X_1$</td>
<td>324.72</td>
<td>1</td>
<td>324.72</td>
<td>808.82</td>
<td>&lt;0.0001</td>
<td>SN</td>
</tr>
<tr>
<td></td>
<td>$X_2$</td>
<td>79.06</td>
<td>1</td>
<td>79.06</td>
<td>196.93</td>
<td>0.0008</td>
<td>SN</td>
</tr>
<tr>
<td></td>
<td>$X_1X_2$</td>
<td>0.029</td>
<td>1</td>
<td>0.029</td>
<td>0.072</td>
<td>0.805</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>$X_1^2$</td>
<td>10.86</td>
<td>1</td>
<td>10.86</td>
<td>27.04</td>
<td>0.013</td>
<td>SN</td>
</tr>
<tr>
<td></td>
<td>$X_2^2$</td>
<td>0.0032</td>
<td>1</td>
<td>0.0032</td>
<td>0.0079</td>
<td>0.934</td>
<td>NS</td>
</tr>
<tr>
<td>Y2</td>
<td>$X_1$</td>
<td>105900</td>
<td>1</td>
<td>105900</td>
<td>406.97</td>
<td>0.003</td>
<td>SN</td>
</tr>
<tr>
<td></td>
<td>$X_2$</td>
<td>30530.67</td>
<td>1</td>
<td>30530.67</td>
<td>117.36</td>
<td>0.001</td>
<td>SN</td>
</tr>
<tr>
<td></td>
<td>$X_1X_2$</td>
<td>9506.25</td>
<td>1</td>
<td>9506.25</td>
<td>36.54</td>
<td>0.009</td>
<td>SN</td>
</tr>
<tr>
<td></td>
<td>$X_1^2$</td>
<td>220.50</td>
<td>1</td>
<td>220.50</td>
<td>0.85</td>
<td>0.425</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>$X_2^2$</td>
<td>128</td>
<td>1</td>
<td>128</td>
<td>0.49</td>
<td>0.533</td>
<td>NS</td>
</tr>
</tbody>
</table>

SS, DF, MS, SN and NS represents sum of square, degree of freedom, mean square difference, significant and non-significant respectively.
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Figure 5.b Comparative in vitro drug release from batches C5-C16; C5 (→-), C6 (→-), C7 (→-), C8 (→-), C9 (→-), C10 (→-), C11 (→-), C12 (→-), C13 (→-), C14 (→-), C15 (→-) and C16 (→-)

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Figure 5.c Overlaid contour plots; $Y_1$ (percentage drug released in 1 h) - - - -, $Y_2$
(time required to release 80% of drug) ....

5.2.3 Evaluation:

5.2.3.1 Percentage drug content:

Captopril granules (2000 mg) of batches C1-C16 were heated at 70±2°C to facilitate leaching of drug in 900 ml of 0.1 N HCl (pH 1.2, 10 min, 100 rpm). The phases were separated after filtering the drug solution. The amount of captopril present in 0.1 N HCl (pH 1.2) was measured spectrophotometrically at
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212 nm wavelength employing UV/visible spectrophotometer (Shimadzu-1700, Pharmaspec, UV 1700, Japan) after suitable dilution.

5.2.3.2 Percentage friability:

Twenty tablets were rotated in a friabilator (Model EF2, Electrolab, Mumbai, India) at 25 rpm for 4 min. The tablets were then dedusted, and the loss in weight due to fracture or abrasion was recorded as percentage weight loss (% friability).

5.2.3.3 In vitro drug release:

The tablets were subjected to in vitro drug release for 12 h in a calibrated USP dissolution test apparatus (Electrolab, Model TDT 06-T, Mumbai, India) equipped with basket employing 900 ml dissolution media. The dissolution media was changed after 2 h from 0.1N HCl (pH 1.2) to phosphate buffer (pH 6.8). The baskets were rotated at 50 rpm and the dissolution medium was maintained at a temperature of 37±0.5°C throughout the experiment.41 Ten ml aliquots were withdrawn and analyzed spectrophotometrically. Ten ml of fresh dissolution medium was added after each withdrawal to maintain the volume of dissolution media. The absorbance of the samples collected at pH 1.2 and 6.8 were measured at wavelengths recommended in I.P 199640 and Nokhodchi et al.41 respectively after suitable dilution against blank with reference to standard calibration curve obtained experimentally (r²=0.99). The UV spectrum of captopril was observed for captopril-excipients interaction.

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Kinetics of drug release:

The method of Bamba et al. was adopted to ascertain kinetics of drug release from the optimized batch C14.\textsuperscript{42} Zero-order, First-order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas and Weibull models were fitted to the dissolution data of batch C14.\textsuperscript{43,48} A FORTRAN software, developed in-house, was used for data fitting. The least value of sum of square of residuals (SSR) and Fisher's ratio (F) were used to select the most appropriate kinetic model.\textsuperscript{48} The results are displayed in Table 5.c.

Table 5.c Results of kinetics of drug release of batch C14

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi model</th>
<th>Hixon-Crowell</th>
<th>Korsmeyer-Peppas</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r^2$</td>
<td>0.944</td>
<td>0.983</td>
<td>0.995</td>
<td>0.979</td>
<td>0.984</td>
<td>0.966</td>
</tr>
<tr>
<td>F*</td>
<td>31.2</td>
<td>12.9</td>
<td>4.91</td>
<td>17.4</td>
<td>4.79</td>
<td>9.33</td>
</tr>
<tr>
<td>SSR*</td>
<td>187.4</td>
<td>77.4</td>
<td>29.4</td>
<td>104.45</td>
<td>23.9</td>
<td>46.6</td>
</tr>
</tbody>
</table>

F* is Fisher's ratio and SSR* is sum of square of residuals
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Similarity factor:

The in vitro drug release data were used for computation of similarity factor ($f_2$) using equation 5.a.\textsuperscript{48-51}

\[
f_2 = 50 \log \left\{ 1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right\}^{-0.5} \times 100
\]

Where $n$ is the number of pull points, $R_i$ is the reference profile at time point $t$ and $T_i$ is the test profile at the same time point. The value of $f_2$ should be between 50 and 100.\textsuperscript{52} The $f_2$ value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases.
5.2.3.4 Fourier transformation infra red spectroscopy study:

Captopril, batch B14 with and without drug (blank) were separately mixed with IR grade potassium bromide. Infrared spectra were taken using an infrared spectrophotometer (Model FTIR-8400S, Shimadzu, Japan) by scanning samples over a wave number of 4000 to 400 cm⁻¹. The results are shown in Figure 5.d.

Figure 5.d Results of fourier transformation study; (a) pure captopril and (b) batch C14 and (c) blank
5.2.4 Criteria for optimized batch:

Two limits were arbitrarily selected; i) $Y_1$: percentage drug released in 1 h should be equal to $25\pm0.5$ and ii) $Y_2$: time required to release 80% of the drug ($t_{80}\%$) should be equal to $518\pm11$ min ($-t_{90}\% = 600\pm12$ min).

5.2.5 Artificial neural network analysis:

Commercial software, Neurosolutions Version 5.0 (NeuroDimension, Inc., Gainesville, FL) was used with a P-4 personal computer. The software combines a modular, icon-based network design interface with an implementation of advanced-learning procedures, such as recurrent back propagation, back propagation through time and genetic optimization. Neurosolutions allows the user to select the number of hidden layers, hidden layer nodes (neurons), iterations used during the model training, learning algorithm, and transfer functions. In the present study, a multi-layer perceptron neural network was used to predict dependent variables ($Y_1=\text{percentage drug released in 1h}$ and $Y_2 = t_{80}\%$, time required to release 80% of the drug) of two batches C14 and C15. The network architecture consisted of two inputs ($X_1$ and $X_2$) and two output ($Y_1$ and $Y_2$) processing elements (PEs) and one hidden layer. The hidden layer contained four PEs with TanhAxon transfer. The learning rule was kept at momentum with step size of 1.0. The output layer contained two PEs with TanhAxon transfer. The learning rule was again kept as momentum with a step size of 0.1. The maximum numbers of epochs allowed were 1000. The program was designed to terminate the training program using minimum function when mean squared error drops below specified threshold of 0.01. The dependent and
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independent variables of \(3^2\) full factorial design (batches C5-C13) were used for training. The dependent \(Y_1\) and \(Y_2\) and independent variables \(X_1\) and \(X_2\) of batches C14 and C15 were used for validation of the trained network.

5.2.6 Average absolute percentage deviation:

The dependent variables \(Y_1\) and \(Y_2\) predicted from the ANN and multiple linear regression analysis was compared with experimental responses using average absolute percentage deviation (AAPD, equation 5.b).

\[
AAPD = \frac{\text{ABS}(E_r - P_r) \times 100}{E_x} \quad \text{--------5.b}
\]

where \(E_r\) and \(P_r\) represent experimental and predicted responses respectively.
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5.3 Results and discussion:

For the development of modified release formulation of freely water soluble drug, hydrophobic polymers are more useful as compared to hydrophilic polymers since they provide advantages such as good stability at varying pH values and moisture levels to well-established safe limits.\(^{53}\) In the last decade, Compritol\(^{\circledR}\) ATO 888 has received keen interest in formulation of modified release formulations.\(^{22-25}\) Compritol\(^{\circledR}\) ATO 888 matrices do not swell in water.\(^{54}\) The aim of the present work was to develop a modified release formulation of captopril which is novel yet industrially acceptable. The pharmaceutical industry is always driven by regulatory requirements. Camphor is a safe material. Camphor water was official preparation in I.P 1955 and was prescribed at dose level of 30 ml containing 0.1% w/v camphor.\(^{55}\) Camphor can easily sublime. Hence, the traces of camphor left in the final formulation are expected to be far less than that described in I.P 1955.\(^{55}\) Menthol is extensively used in the preparation of peppermints and cough syrups. Menthol is a sublimable material. The WHO acceptable daily intake of menthol, for 70 kg adult, is 28 mg.\(^{56}\) Menthol is well known intestinal and dermal permeability enhancer leading to improvement in oral bioavailability.\(^{38-39}\) Hence, the use of eutectic mixture of camphor and menthol in formulation of pharmaceutical dosage form can be advantageous. Recovery of camphor and menthol is not mandatory as in the case of organic solvents. Special equipments are not required for processing of the formulation and the traces left in final formulation may improve permeability, taste and odour of the product. Captopril falls under biopharmaceutical
classification system (BCS) class III drug. Hence, it is expected that presence of traces of menthol in the formulation may improve permeation of the drug and subsequently improve oral bioavailability. The amount of captopril in the formulated batches C1-C16 was 50 mg. The percentage drug content in the batches (C1-C15) prepared using eutectic mixture of menthol and camphor was uniform (>95±3%). The physical mixture of captopril, Compritol® ATO 888 and ethyl cellulose (batch C16) with the concentration equivalent to that of batch C14 showed drug content of 78±5%. Incomplete solid-solid mixing of the formulation components could be the probable reason for lower drug content in case of batch C16. Uniform solid-solid mixing is more difficult to achieve than liquid-liquid mixing (used in batch C1-15) mainly due to size and density differences. The UV spectrum of captopril before and after processing of the formulation remained unchanged indicating stability of the drug during processing.

In the present work, t80% was used in place of t90% as one of the dependent variable since; batch C13 showed in complete drug release (<82% in 12h) preventing the prediction of the responses using factorial design in optimization study. The percentage friability of tablets of batches C1-C16 was within the acceptable limits (<1%).

5.3.1 Preliminary studies:

The UV spectrum of the drug remained unchanged during in vitro drug release, indicating stability of captopril during study. Figure 5.a shows drug release profile of preliminary batches of tablets containing different ratio of captopril to Compritol® ATO 888 (1:1-1:4). Figure 5.a demonstrates that the
captopril release rate was influenced by the amount of Compritol® ATO 888 in the formulation. Slowest drug release was observed from the tablets containing 1:4 ratio of Compritol® ATO 888. Complete drug release was observed from batches C1-C4 in less than 420 min. The time required to release 80% of the drug ($t_{80\%}$) from batches C1-C4 were 155, 186, 240 and 287 min respectively. The probable reason for relatively faster drug release could be high aqueous solubility of captopril. The tablets of batches C1-C4 maintained their integrity during the in vitro drug release study highlighting the fact the drug release might controlled by diffusion mechanism. Considering the cost of Compritol® ATO 888, the ratio of captopril to Compritol® ATO 888 was not increased above 1:4, and relatively cheap water insoluble polymer (ethyl cellulose) was added as extragranular fraction in the subsequent trials to modulate the drug release.

5.3.2 Factorial Design:

A two factor, three level full factorial design was used for optimization of the formulation using ratio of captopril and Compritol® ATO 888 ($X_1$) and amount of ethyl cellulose ($X_2$) as independent variables. Table 5.a shows the design layout, ranges and responses of the formulated batches and Figure 5.b shows the in vitro drug release profiles. The responses ($Y_1$= percentage drug released in 1 h and $Y_2$ = time required to release 80% of the drug) varied from 20-42% and 280-705 min respectively. The results of analysis of variance (ANOVA) for the responses $Y_1$ and $Y_2$ are shown in Table 5.b. Based on the results of ANOVA, it is concluded that the full model incorporating terms $X_1$, $X_2$, $X_1X_2$, $X_1^2$ and $X_2^2$ is unnecessary, and that refined models including fewer significant terms ($p<0.05$)
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will be appropriate. For response $Y_1$, the terms $X_1$, $X_2$ and $X_1^2$ are significant ($p<0.05$) whereas for the response $Y_2$, the terms $X_1$ and $X_2$ and $X_1X_2$ are significant ($p<0.05$).

In order to make prediction of responses ($Y_1$ and $Y_2$), mathematical models were evolved omitting the insignificant terms by adopting multiple regression analysis. Equations 5.c and 5.d represents refined models for responses $Y_1$ and $Y_2$ with the values of $R^2$ and Fisher’s ratio ($F$).

$Y_1 = 29.07 - 7.35X_1 - 3.63X_2 + 2.33X_1^2$ — 5.c

($R^2 = 0.992, F = 215, p<<0.05$)

$Y_2 = 439 + 132.83X_1 + 71.33X_2 + 48.75X_1X_2$ — 5.d

($R^2 = 0.997, F = 558, p<<0.05$)

As the interaction/polynomial terms are significant, the conclusions cannot be drawn by considering the magnitude of coefficient of the main effects $X_1$ and $X_2$. Hence, contour plots were drawn to investigate the influence of significant variables.

The critical observation of the overlaid contour plots of $Y_1$ and $Y_2$ (Figure 5.c) reveals that by varying $X_1$ from 0.14 to 0.2 and $X_2$ from 0.7 to 0.8 one can achieve desired region of acceptability in terms of $Y_1$ ($25\pm0.5$) and $Y_2$ ($518\pm11$ min). A check-point batch (Table 5.a, C14) was formulated. An additional check-point batch C15, lying outside the region of acceptability (but within the design space), was also formulated for model validation. The theoretical and experimental responses of $Y_1$ and $Y_2$ for batch C14 were 25.5%; 512 min and
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24.7%; 520 min respectively whereas that of batch C15 were 23.9%; 567 min and 23.2%; 543 min respectively indicating predictive capability of the evolved models. Looking to the results of in vitro drug release, batch C14 was considered as an optimized batch satisfying predetermined criteria in terms of percentage drug released in 1 h \( (Y_1) \) and time required to release 80% of the drug \( (Y_2 = t_{80}) \).

The in vitro drug release data from 0-70% drug release of batch C14 were analyzed for determining kinetics of drug release. Model fitting was done using an in-house computer program, in FORTRAN language, developed by the authors. Zero-order, first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models were tested. Table 5.c shows that kinetics of drug release was best explained by Korsmeyer-Peppas model with least Fisher's ratio \( (F) \) and sum of square of residuals \( (SSR) \). The value of diffusion coefficient \( (n) \) was 0.52 indicating non-fickian mechanism of drug release.

To study the influence of processing, batch C16 containing physical mixture of formulation excipient was formulated and its in vitro drug release was compared with batch C14 (Figure 5.b). The drug release from batch C16 was faster than batch C14 with \( Y_1 \) and \( Y_2 \) of 36.7% and 335 min respectively. Complete drug release from batch C16 was observed within 490 min. The in vitro drug release profile of batch C14 and C16 were dissimilar \( (f^2=40) \). Probable reason for this behaviour could be due to covering of the drug particles by Compritol® ATO 888 in batch C14.
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The infrared spectra of captopril, granules of batch C14 with and without drug (blank) are shown in Figure 5.d. The infrared spectra of captopril and samples of batch C14 were comparable. Captopril showed two prominent peaks at 1745.46 cm\(^{-1}\) and 2565.15 cm\(^{-1}\) because of presence of carboxyl and thiol groups respectively. These peaks were retained in sample of batch C14 containing drug and absent in blank indicating presence and stability of captopril during processing.

5.3.3 Artificial neural network:

During development of pharmaceutical dosage form, optimization of formulation variables is very critical. Multiple linear regression analysis is widely used method for optimization.\(^{57-58}\) However, since, the prediction of pharmaceutical responses based on polynomial equation of multiple linear regressions (MLR) is often limited to low levels; prediction power of the MLR is poor. To overcome disadvantages of MLR, artificial neural networks were introduced.\(^{59-60}\)

Artificial neural networks (ANN) are highly distributed interconnections of adaptive nonlinear processing elements (PEs). When implemented in digital hardware, the PE is a simple sum of products followed by nonlinearity (McCulloch-Pitts neuron). The connection strengths of PEs are adapted to match networks output with desired response. Different type of artificial neural networks like multilayer perceptron, generalized feed forward, modular neural network, Jordan/Elman network, principal component analysis, generalized regression
neural network, self organizing feature map network, time lag recurrent network, recurrent network, fuzzy logic network, etc are available for prediction. In the present study, multi-layer perceptron was used. Multi-layer perceptrons are layered feed forward networks typically trained with static back propagation. The dependent ($Y_1$ and $Y_2$) and independent variables ($X_1$ and $X_2$) of $3^2$ full factorial design (batches C5-C13) were used for training whereas that of batches C14 and C15 were used for validation of the trained network. Predicted ANN responses of $Y_1$ and $Y_2$ of batches 14 and C15 were 25.0%; 523.1 min and 23.3%; 568.8 min respectively indicating no significant difference between predicted and practical responses.

5.3.4 Comparison of ANN and factorial design:

Both ANN and factorial design visualized similar results, and their predictions regarding the responses $Y_1$ and $Y_2$ coincided very well. Statistically, the practical and predicted responses of batches C14 and C15 was insignificant with $F_{\text{calculated}} < F_{\text{critical}}$ at 5% level of significance. The average absolute percentage deviation (AAPD) obtained from ANN for $Y_1$ and $Y_2$ were 0.99 and 2.67 respectively whereas that of multiple regression analysis were 3.33 and 2.97 respectively indicating higher prediction power of ANN.
5.4 Conclusion:

Modified release oral captopril formulation was developed using Compritol® ATO 888 and ethyl cellulose as rate limiting polymers. Novel use of eutectic blend in the formulation of modified release product is demonstrated. The required drug release can be obtained by altering formulation and/or processing conditions. The concept of quality by design (QBD) was adopted. The optimized formulations by-pass the existing patents on sustained release captopril. Finally, the process can be easily adopted by industry. The kinetics of the drug release from optimized batch containing 50 mg captopril, 160 mg Compritol® ATO 888 and 220 mg ethyl cellulose was best explained by Korsmeyer-Peppas model.
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5.5 References:


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40. The Indian Pharmacopoeia, Govt. of India, Ministry of Health and Family Welfare, The Controller of Publication, New Delhi, 1996.


47. Higuchi I. Analysis of data on the medicament release from ointments. J. Pharm. Sci. 1962, 51(8), 802-804.
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