IMPLEMENTATION OF QBD IN FORMULATION OF MICROEMULSION BASED IN-SITU GELLING SYSTEM OF ANTIMIGRAIN DRUG

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Abstract: Oral route of drug administration is perhaps the most preferred route for the delivery of drugs. The various dosage forms like films, sprays, tablets, gels etc. are administered in buccal cavity for systemic effect. Spray based systems are preferred dosage form because of ease of administration, accurate dosage, self-medication, pain avoidance and patient compliance. In buccal spray based system the drug is in contact with buccal mucosa and the drug released and absorbed fast from the buccal mucosa which is rich in blood supply. Microemulsion based in situ gelling system for treatment of migraine has proved to be promising drug delivery system. Developed microemulsion based in situ gelling system was evaluated for percent cumulative drug release, Mucoadhesive strength, Viscosity, pH, Drug content, Drop test, Sprayability, Centrifugation. The optimization of the best trial batch was done using software Expert Design 9.0.3.1.

Keywords: Microemulsion, In-situ gelling system, Rizatriptan benzoate, Pseudoternary phase diagram, Optimization, QBD.

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INTRODUCTION

Conventional drug delivery systems have many of the disadvantages as first pass metabolism, instability in acidic environment, drug degradation in gastrointestinal environment and poor pharmacological response resulting into inadequate and erratic oral absorption. These difficulties can be overcome by designing a mucoadhesive Drug Delivery Systems. It includes buccal drug delivery system, nasal drug delivery system, ophthalmic drug delivery system etc. BDDS is a mucoadhesive drug delivery system wherein the dosage form comes in intimate contact with the mucous membrane of the buccal cavity lining the inside of the cheeks. It is most advantageous because of abundant blood supply in the buccal mucosa, increased residence time, easy accessibility and direct access to the systemic circulation. Conventional liquid dosage forms for mucosal delivery shows lower retention at the site of absorption. Preformed gels overcome this disadvantage but show dosage non-uniformity due to difficulty in application. In situ gelling system has significant advantages over preformed gels for buccal drug delivery, due to ease of sprayability and reproducibility in dosing. Triggers for formation of in situ gel include pH change, ions and temperature shift and also contact with water. Microemulsions are known to exhibit gel formation under certain conditions. This gel formation may be caused by water molecules adsorbed or intercalated between the hydrophilic chains of surfactants via hydrogen bonding which result in less mobile and regular gel structure. Rizatriptan benzoate is belonging from a class of triptan used in treatment of migraine and is considered more effective than the traditional triptans for the treatment of acute migraine attacks. Microemulsion based in situ gelling system for antimigrain drug shows enhanced retention, rapid onset of action and enhanced bioavailability.

MATERIALS AND METHODS:

Rizatriptan benzoate (RTBZ) was obtained as gift sample from Alkem Laboratories (Taloja MIDC Navi Mumbai); Capmul MCM was obtained as gift sample from Abitec Corporation, Mumbai. Transcutol HP, Maisine 35-1, Labrasol was obtained from Gattefosse India Pvt. Ltd. Mumbai. Propylene glycol dicaprylate/dicaprate (PGDD) was obtained from Subhash chemical industries Pvt. Ltd. MIDC, Pune. Tween 80, Tween 20, Oleic acid, Propylene glycol, Glycerol was purchased from S.D. fine Chemicals Mumbai. All chemicals and solvents used were of analytical grade.

Experimental:

Calculation of dose of RTBZ:

Marketed single dose of rizatriptan is available as 5 mg and 10 mg. As rizatriptan is in salt form (rizatriptan benzoate) so the quantity of drug taken for the formulation can be calculated as:

Molecular weight of rizatriptan benzoate: 391.47
Molecular weight of rizatriptan: 269.4

Factor: $\frac{391.47}{269.4} = 1.453$

Actual quantity of rizatriptan benzoate taken = $1.453 \times \text{Dose}$

10 mg dose provides greater effect than 5 mg dose but side effects associated are generally higher.

The Marketed tablet formulations available are of 10 mg or 5 mg. Since we are administering via buccal route drug is bioavailable 100 % and oral bioavailability of drug is 45 %. The dose 2.5 mg has been selected.

Actual quantity of rizatriptan benzoate taken = $1.453 \times \text{Dose}$

\[= 1.453 \times 2.5\]

\[= 3.6325 \text{ mg/dose}\]

\[= 3.6325 \text{ mg/ml}\]

**Preformulation Studies:**

**Selection of Oil, surfactants & co surfactants for microemulsion:**

Solubility of rizatriptan benzoate in various oils (Oleic acid, Maisine, PGDD, Capmul MCM), surfactants (Tween 20, Tween 80, Kolliphor EL, Transcutol, Labrasol) and Co-surfactants (Glycerol, Propylene glycol) was determined by adding an excess amount of rizatriptan benzoate in 1 ml of each oil, surfactant and co surfactant.

![Fig 1: Solubility of Rizatriptan benzoate](image-url)
Construction of phase diagrams:

Pseudo ternary phase diagrams for different microemulsion systems were developed using the aqueous titration method to identify microemulsion region, viscous region and gel region. Volumes of each surfactant and co-surfactant mixture were blended with oil in a ratio of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 a transparent and homogenous mixture of oil and surfactant/Co-surfactant (S/CoS) was formed by vortexing for 5 min. Then each mixture was titrated with distilled water in a drop wise manner and visually observed for turbidity which indicates the end of microemulsion region. Mixtures were carefully observed for viscous and gel regions. Pseudo ternary phase diagrams were constructed using TriDraw software.

Preparation of in situ gelling mucoadhesive microemulsion:

On the basis of the solubility studies, oil, surfactants and co-surfactants were selected. Distilled water was used as an aqueous phase for titration. Surfactant and co-surfactant (Smix) were mixed at different ratios. Predetermined amounts of the drug were dissolved in the required quantity of oil. Surfactant and co-surfactant were added to the above mixture as fixed ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1). Distilled water was added gradually with continuous stirring on vortex mixer clear, formulations were indicative of stable micro emulsions. Microemulsion based in-situ gelling region is identified as the region containing microemulsion compositions that gel rapidly on contact with minute quantities of water.

Table 1: Composition of formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Oil (ml)</th>
<th>Surfactant : Co surfactant (ml)</th>
<th>Qty of water for 10 ml system</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 4</td>
<td>Capmul MCM (4ml)</td>
<td>Tween 80: Propylene glycol (3:1)</td>
<td>6 ml</td>
</tr>
<tr>
<td>A 6</td>
<td>Capmul MCM (4ml)</td>
<td>Tween 80: Propylene glycol (2:1)</td>
<td>6.5 ml</td>
</tr>
<tr>
<td>A 8</td>
<td>Oleic acid (2ml)</td>
<td>Tween 80: Propylene glycol (2.5:1)</td>
<td>1.5 ml</td>
</tr>
<tr>
<td>A 11</td>
<td>Oleic acid (2ml)</td>
<td>Tween 80: Propylene glycol (2:1)</td>
<td>2 ml</td>
</tr>
<tr>
<td>A 12</td>
<td>Oleic acid (2ml)</td>
<td>Tween 80: Propylene glycol (3:1)</td>
<td>2.5 ml</td>
</tr>
</tbody>
</table>

Drug: 36.325 mg/ml

Characterization of microemulsion based in-situ gelling system:

Visual inspection (Appearance): in situ gelling mucoadhesive microemulsion was observed for homogeneity, optical clarity and fluidity.

pH:
The pH of the samples were measured by using ELICO, LI 120, pH meter India. pH was measured by directly immersing the electrode of the pH meter in the system.

**Viscosity:**

Viscosity of in situ gelling mucoadhesive microemulsion was measured by Brookfield Viscometer (LVII, Brookfield Inc., USA) at 50 RPM. The viscosity with the spindle No. 3, 4 and 5 for Microemulsions, viscous systems and gelled systems respectively at 50 RPM. The measurement was performed at ambient temperature in triplicate.

**Measurement of mucoadhesive strength:**

The strength of bond formed between the formulation and mucosal membrane excised from goat buccal mucosa was determined using two-arm balance method.

Fresh goat buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The membrane was washed with distilled water and then with pH 6.8 phosphate buffer as a moistening fluid. The two sides of the balance were balanced with 8.840 g weight on the right hand side. The entire setup of the assembly is shown in Fig.2.

Force of adhesion (N) = (Mucoadhesive strength (g) * 9.81) / 1000

Bond strength (N/m²) = Force of adhesion / surface area of the vial

The experiment was carried out for Microemulsion, viscous systems and gelled systems in triplicates of all the formulations.
Drug content:

% drug content of all formulations was determined UV spectroscopically by making suitable dilutions at 280 nm.

% Cumulative drug release:

The drug release from in situ gelling mucoadhesive microemulsion was determined using Franz diffusion cell. The diffusion medium used was pH 6.8 phosphate buffer, maintained at 37 ± 0.5°. The samples were analyzed spectrophotometrically after appropriate dilution at 280 nm. The test was performed in triplicates. A graph of % cumulative drug release versus time is plotted.

Drop test:

A drop of in-situ gelling mucoadhesive microemulsion formulation was added to a beaker containing water (50 ml) and observed for gelling.

Centrifugation: ME formulations were centrifuged at 6000 rpm for 15 min and observed if any phase separation is there.

Sprayability: The spray pattern test is done to access equivalent drug deposition pattern resulting in equivalent delivery of the drug.

• Spray pattern: The spray pattern was checked by incorporating a colored dye in formulations and spraying it on a sheet of paper held at distance of 4 cm vertically from the spray.

Dilution potential: The ability of the in-situ gelling formulation to form clear solution when diluted with water and vortexed to dissolve the gel were tested and solution was stored for 48 hrs to detect any change in solubilization capacity of ME. One dose diluted to 50 ml distilled water and stored.

RESULT AND DISCUSSIONS:

Pseudoternary phase diagrams:

Phase diagrams were obtained using the oils, surfactants and co-surfactants. Compositions containing oil phase, surfactant and co-surfactant, revealed the microemulsion based in-situ gelling region. The in-situ gelling region comprised of the compositions which would gel instantaneously on contact with minimum amounts of water, and demonstrated the maximum viscosity was thus selected for incorporation of rizatriptan benzoate. Titration with water was done for oil, surfactant-co surfactant mixture, and was carefully observed for ME, viscous and gel region (Fig 5).
Visual assessment:

**Fig 3: Gelling of ME formulations**

Microemulsion formulations prepared were found to be optically clear, transparent faint yellow colored homogenous liquids (Table 2).

**pH:**

pH of the mucoadhesive microemulsions found near to natural pH of buccal cavity, in the range of 6.66 to 6.90 (Table 2).

**Drug content:**

The percentage of drug content of all the formulations varied from 97.15% to 99.75% as shown in (Table 2). This result indicates that there was uniform distribution of the drug throughout the batch.

**Drop test (Beaker method):**

When added in a water containing beaker, formulation gels immediately and settles down at the bottom of the beaker (fig 3).

**Table 2: pH, Drug content, Appearance, In-vitro gelling and Sprayability results**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>pH (n=3)</th>
<th>%Drug content (n=3)</th>
<th>Appearance</th>
<th>Drop test</th>
<th>Sprayability</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 4</td>
<td>6.66±0.03</td>
<td>99.16 ± 0.5</td>
<td>Transparent</td>
<td>Gels immediately</td>
<td>++</td>
</tr>
<tr>
<td>A 6</td>
<td>6.61±0.01</td>
<td>98.82 ± 0.3</td>
<td>Transparent</td>
<td>Gels immediately</td>
<td>+++</td>
</tr>
<tr>
<td>A 8</td>
<td>6.90±0.01</td>
<td>99.75 ± 0.2</td>
<td>Transparent</td>
<td>Gels immediately</td>
<td>+++</td>
</tr>
<tr>
<td>A 11</td>
<td>6.76±0.005</td>
<td>97.58 ± 0.2</td>
<td>Transparent</td>
<td>Gels in few seconds</td>
<td>++</td>
</tr>
<tr>
<td>A 12</td>
<td>6.77±0.01</td>
<td>97.15 ± 0.2</td>
<td>Transparent</td>
<td>Gels in few seconds</td>
<td>++</td>
</tr>
</tbody>
</table>
% Cumulative drug release:

The results of drug release studies from in-situ gelling mucoadhesive microemulsion are shown in table 3 and Fig. 4. Incorporation of drug in microemulsion-based system improved drug solubilization and in vitro release.

Table 3: % CR of drug at different time intervals

<table>
<thead>
<tr>
<th>Formulation</th>
<th>15 min</th>
<th>30 min</th>
<th>45 min</th>
<th>60 min</th>
<th>75 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 4</td>
<td>10.96±0.08</td>
<td>37.02±0.39</td>
<td>48.98±0.04</td>
<td>60.69±0.03</td>
<td>72.9±0.06</td>
<td>82.19±0.10</td>
</tr>
<tr>
<td>A 6</td>
<td>10.79±0.07</td>
<td>35.95±0.07</td>
<td>46.9±0.07</td>
<td>58.8±0.09</td>
<td>68.72±0.06</td>
<td>80.47±0.05</td>
</tr>
<tr>
<td>A 8</td>
<td>15.33±0.19</td>
<td>42.87±0.06</td>
<td>56.29±0.11</td>
<td>67.97±0.07</td>
<td>79.14±0.08</td>
<td>88.8±0.04</td>
</tr>
<tr>
<td>A 11</td>
<td>2.56±0.49</td>
<td>24.23±0.54</td>
<td>36.12±0.12</td>
<td>50.32±0.37</td>
<td>64.37±0.15</td>
<td>84.81±0.12</td>
</tr>
<tr>
<td>A 12</td>
<td>2.53±0.09</td>
<td>23.03±0.08</td>
<td>35.32±0.11</td>
<td>47.95±0.26</td>
<td>60.46±0.15</td>
<td>80.69±0.32</td>
</tr>
</tbody>
</table>

Fig 4: % CR of drug from formulations
**Table 4: Viscosity of formulations**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Viscosity (Spindle no.) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original ME (3)</td>
</tr>
<tr>
<td>A 4</td>
<td>270 ±10</td>
</tr>
<tr>
<td>A 6</td>
<td>253.33±11.54</td>
</tr>
<tr>
<td>A 8</td>
<td>293.33±11.54</td>
</tr>
<tr>
<td>A 11</td>
<td>233.33±11.54</td>
</tr>
<tr>
<td>A 12</td>
<td>253.33±5.77</td>
</tr>
</tbody>
</table>

**Fig 5: Pseudoternary phase diagrams**

Blue: ME region

Orange: Viscous region
Centrifugation: No phase separation or visual changes appear. All formulations were found to be stable.

Dilution potential: When diluted with water and stored for 48 hrs, no visible signs of precipitation occurred.

Sprayability: The spray pattern followed by formulations showed in fig 6.

Viscosity and mucoadhesive strength:

Viscosity and mucoadhesive strength of microemulsions, viscous systems and gelled systems showed in table 4 and 5 respectively. Viscosity and mucoadhesion shown increase value on increasing amount of water.

**Table 5: Mucoadhesion properties of formulation**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Mucoadhesive strength (gm)</th>
<th>Force of adhesion (N)</th>
<th>Bond strength (N/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original ME</td>
<td>22.55 ±0.25</td>
<td>0.22±0.002</td>
<td>0.10±0.001</td>
</tr>
<tr>
<td>A 4 Viscous ME</td>
<td>32.92±0.12</td>
<td>0.32±0.001</td>
<td>0.14±0.000</td>
</tr>
<tr>
<td>Gelled ME</td>
<td>40.83±0.59</td>
<td>0.40±0.005</td>
<td>0.18±0.002</td>
</tr>
<tr>
<td>Original ME</td>
<td>22.71±0.20</td>
<td>0.22±0.002</td>
<td>0.10±0.001</td>
</tr>
<tr>
<td>A 6 Viscous</td>
<td>32.93±0.44</td>
<td>0.32±0.004</td>
<td>0.14±0.001</td>
</tr>
<tr>
<td>Gelled</td>
<td>37.94±0.16</td>
<td>0.37±0.001</td>
<td>0.16±0.000</td>
</tr>
</tbody>
</table>
### Table 1: Mucoadhesive Strength of Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Original ME</th>
<th>Viscous ME</th>
<th>Gelled ME</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 8</td>
<td>35.26±0.37</td>
<td>43.67±0.28</td>
<td>54.60±0.17</td>
</tr>
<tr>
<td></td>
<td>0.34±0.003</td>
<td>0.42±0.00</td>
<td>0.53±0.001</td>
</tr>
<tr>
<td></td>
<td>0.15±0.001</td>
<td>0.19±0.001</td>
<td>0.24±0.00</td>
</tr>
<tr>
<td>A 11</td>
<td>8.83±0.18</td>
<td>15.78±0.33</td>
<td>26.25±0.02</td>
</tr>
<tr>
<td></td>
<td>0.08±0.001</td>
<td>0.15±0.003</td>
<td>0.25±0.000</td>
</tr>
<tr>
<td></td>
<td>0.03±0.000</td>
<td>0.07±0.001</td>
<td>0.11±0.0001</td>
</tr>
<tr>
<td>A 12</td>
<td>7.40±0.25</td>
<td>16.75±0.15</td>
<td>25.62±0.25</td>
</tr>
<tr>
<td></td>
<td>0.07±0.002</td>
<td>0.16±0.001</td>
<td>0.25±0.002</td>
</tr>
<tr>
<td></td>
<td>0.03±0.001</td>
<td>0.07±0.000</td>
<td>0.11±0.001</td>
</tr>
</tbody>
</table>

**Optimization:**

A $2^2$ randomized full factorial design was selected for formulation A 8 and the two factors were evaluated, each at 2 levels and experimental trials were performed on all 4 possible combinations by using Stat Ease design Expert 9.0.3.1. software. The amounts of Tween 80 (X1) and Propylene glycol (X2) were selected as independent variables. The responses % cumulative drug release and mucoadhesive strength were selected as dependent variables. Regression polynomials for the individual dependent variables were calculated with the help of Design Expert software and applied to approximate the surface response contour plots.

**Surface response plot:** The quadratic model obtained from the regression analysis is used to build a 3-D graph in which the responses were represented by curvature surface as a function of independent variables presented in Fig 13 and 15. The relation between the responses and independent variables can be directly visualized from the surface response plots. Graphical
presentation of the data helped to show the relationship between the response and independent variables. The information given by the graphs is an interpretation of the mathematical equations obtained from statistical analysis.

**Contour plots**: A contour plot is a graphical technique for representing a 3-dimensional surface by plotting constant z slices, called contours, on a 2-dimensional format. That is, given a value for z, coordinates where that z value occurs. The contour plot is an alternative to 3-D surface plot (fig 14 and 16).

**Overlay plot**: Among the different solutions obtained, the formulation containing 3 ml tween 80, and 1.5 ml propylene glycol was selected as optimized formulation (fig 17).

### Table 6: Composition of optimization Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Oil</th>
<th>Surf:Cosurf</th>
<th>Distilled water</th>
<th>Na-Metabisulphite</th>
<th>Propyl paraben</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1</td>
<td>Oleic acid 2ml</td>
<td>Tween 80+PG (3:0.5) 8ml</td>
<td>1.5 ml</td>
<td>0.1%</td>
<td>0.02%</td>
</tr>
<tr>
<td>F 2</td>
<td>Oleic acid 2ml</td>
<td>Tween 80+PG (2:1.5) 8ml</td>
<td>1.5 ml</td>
<td>0.1%</td>
<td>0.02%</td>
</tr>
<tr>
<td>F 3</td>
<td>Oleic acid 2ml</td>
<td>Tween 80+PG (3:1.5) 8ml</td>
<td>1 ml</td>
<td>0.1%</td>
<td>0.02%</td>
</tr>
<tr>
<td>F 4</td>
<td>Oleic acid 2ml</td>
<td>Tween 80+PG (2:0.5) 8ml</td>
<td>1.5 ml</td>
<td>0.1%</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

**Drug**: 36.325 mg/ml

**Characterization of optimized formulation**: Characterization was done as it is done for trial formulations.

**RESULT AND DISCUSSION:**

**Pseudoternary phase diagram**: Pseudoternary phase diagrams for optimization formulations are shown in fig 8.

**Visual assessment**:

Microemulsion formulations prepared were found to be optically clear, transparent faint yellow colored homogenous liquids (Table 7).

**pH**:

pH of the mucoadhesive microemulsions found near to natural pH of buccal cavity, in the range of 6.81 to 6.85 (Table 7).
Drug content:
The percentage of drug content of all the formulations varied from 98.79% to 99.98% as shown in (Table 7). This result indicates that there was uniform distribution of the drug throughout the batch.

Drop test (Beaker method):
When added in a water containing beaker, formulation gels immediately and settles down at the bottom of the beaker (fig 9).

% Cumulative drug release:
The results of drug release studies from in situ gelling mucoadhesive microemulsion are shown in table 8 and Fig. 10. Incorporation of drug in microemulsion-based system improved drug solubilization and in vitro release. Formulations F 2 and F 3 showed maximum drug release in 60 min.

Centrifugation: No phase separation or visual changes appear. All formulations were found to be stable.

Dilution potential: When diluted with water and stored for 48 hrs, no visible signs of drug precipitation occurred.

Sprayability: The spray pattern followed by formulations showed in fig.11

Viscosity and mucoadhesive strength:
Viscosity and mucoadhesive strength of microemulsions, viscous systems and gelled systems showed in table 9 and fig 12 respectively. Viscosity and mucoadhesion shown increase value on increasing amount of water.
Table 7: pH, Drug content, Appearance, In-vitro gelling and Spray ability results

<table>
<thead>
<tr>
<th>Formulation</th>
<th>pH (n=3)</th>
<th>% Drug content (n=3)</th>
<th>Appearance</th>
<th>Drop test</th>
<th>Sprayability</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 1</td>
<td>6.85 ±0.13</td>
<td>98.79 ± 0.17</td>
<td>Transparent faint yellow</td>
<td>Gels immediately</td>
<td>+++</td>
</tr>
<tr>
<td>F 2</td>
<td>6.81 ±0.01</td>
<td>99.92 ± 0.09</td>
<td>Transparent faint yellow</td>
<td>Gels immediately</td>
<td>+++</td>
</tr>
<tr>
<td>F 3</td>
<td>6.82 ± 0.01</td>
<td>99.98 ± 0.04</td>
<td>Transparent faint yellow</td>
<td>Gels immediately</td>
<td>+++</td>
</tr>
<tr>
<td>F 4</td>
<td>6.83 ± 0.01</td>
<td>98.99 ± 0.04</td>
<td>Transparent faint yellow</td>
<td>Gels immediately</td>
<td>+++</td>
</tr>
</tbody>
</table>

Table 8: % CR of drug at different time intervals

<table>
<thead>
<tr>
<th>% Cumulative drug release (CR) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>F 1</td>
</tr>
<tr>
<td>F 2</td>
</tr>
<tr>
<td>F 3</td>
</tr>
<tr>
<td>F 4</td>
</tr>
</tbody>
</table>
Fig 10: % CR of drug from formulations

Fig 11: Sprayability of formulations

Table 9: Viscosity of formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Viscosity (Spindle no.) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original ME (3)</td>
</tr>
<tr>
<td>F 1</td>
<td>300 ±0.00</td>
</tr>
<tr>
<td>F 2</td>
<td>340±0.00</td>
</tr>
<tr>
<td>F 3</td>
<td>376.6667±5.77</td>
</tr>
<tr>
<td>F 4</td>
<td>316.6667±15.27</td>
</tr>
</tbody>
</table>
**Fig 12:** Mucoadhesive strength of formulations

**Fig. 13:** 3-D surface plot of % cumulative drug release

Design-Expert® Software  
Factor Coding: Actual  
Cumulative drug release (%)  
92.7946  
81.2593  
X1 = A: Tween 80  
X2 = B: Propylene glycol  

Cumulative drug release (%)  
A: Tween 80 (ml)  
B: Propylene glycol (ml)  
1.5  
2  
2.5  
3  
0.75  
1  
1.25  
2.25  
2.5  
2.75  
3.0  

Available Online at www.ijprbs.com
Fig. 14: Contour plot of % cumulative drug release

Fig. 15: 3-D surface plot of mucoadhesive strength
Fig. 16: contour plot of mucoadhesive strength

Fig 17: Overlay plot
REFERENCES:

1. Kumar V, Aggarwal G, Zakir F, Choudhary A; Buccal Bioadhesive Drug Delivery- A Novel Technique; International Journal of Pharmacy and Biological Sciences; 2011; 1(3); 89-102.


