Design, Preparation And Evaluation Of Colon Targeted Tablets Of Budesonide

Shrikrishna D. Gite, Kishor S. Salunkhe, Raosaheb S. Shende

Abstract: The present research was undertaken to prepare colon targeted tablets for budesonide containing solid self nanoemulsifying drug delivery system (SNEDDS). The liquid SNEDDS was prepared by taking selected concentration of Capmul MCM C8, tween 80 and polyethylene glycol 400 from ternary phase diagram. The prepared liquid SNEDDS formulations were evaluated by microscopy, dilution test, particle size measurement, zeta potential, and stability study to select the optimized formulation. The optimized liquid SNEDDS was converted to solid by adding absorbent and drying in oven. The resulting solid SNEDDS was evaluated for drug content and micromeric properties. Finally, coated tablets of solid SNEDDS for targeting colon were prepared and evaluated for drug release. The ternary phase diagram was constructed to select concentration of components. The optimized formulation was found transparent, no phase separation, and stable to dilution, centrifugation and temperature. Moreover, droplet size was observed 247.8 nm, polydispersity index 0.155 and zeta potential -5.43 mV. The drug content of solid SNEDDS was 99.37% and showed good flow properties. The prepared coated tablets containing solid SNEDDS for colon targeting exhibited 98.11% drug release. Hence, colon targeted drug delivery containing solid SNEDDS of budesonide was prepared and evaluated which may provide path to develop such system other poorly water soluble drugs also.

Index Terms: Budesonide, colon targeted tablet, self nanoemulsifying drug delivery, ternary phase diagram, zeta potential

1 INTRODUCTION

The Colon-targeted drug delivery has been well established due to its potential to improve treatment of local diseases affecting the colon and reducing systemic side effects [1]. Some diseases which affect the colon include Crohn’s disease, ulcerative colitis, and irritable bowel syndrome, colonic cancer etc. The delivery of drug to the colon without being absorbed first in the upper gastrointestinal tract allows for a higher concentration of the drug to reach the colon with minimal systemic absorption [2]. The colon has become ideal site for drug delivery due to long retention time of colonic contents and ability of colonic mucosa to enhance the absorption of drugs. Oral dosage forms are the preferred delivery route for colon-targeted delivery due to ease of administration, convenience, safety [3], [4]. The Self nanoemulsifying drug delivery system (SNEDDS) is composed of with a peculiar isotropic mixture of lipids and surface coating emulsion. These systems with drugs particles size less than 100 nm appear optically clear and thermodynamically stable. SNEDDS enhances the permeability of drug through biological membrane [5]. SNEDDS spread readily in vivo and motility of the stomach and the intestine causes self-emulsification. Rapid emulsion formation aids to keep the drug in soluble form whereas the greater surface area provided by the small droplets facilitates more effective drug transport through the membrane leading to improved oral bioavailability [6]. Thus a SNEDDS containing budesonide could increase its solubility and permeability into the tissue and cells at the site of inflammation [7]. Budesonide is a locally acting corticosteroid with high affinity for glucocorticoid receptors. The therapeutic advantages of budesonide are negligible oral bioavailability, rapid clearance and no formation of active metabolites [8]. Hence, it is preferred over old steroids such as hydrocortisone, prednisolone and dexamethasone for the localized treatment of inflammatory bowel diseases. However, budesonide suffer from poor solubility and bioavailability, which limits its dissolution and therapeutic potential. Therefore, there is strong need to improve the budesonide solubility and develop formulation for effective drug targeting [9]. Accordingly, SNEDDS of budesonide was prepared, transformed to solid form and its colon targeted tablets were formulated and evaluated.

2 MATERIALS AND METHODS

Budesonide was received as gift sample from Wockhardt Ltd. Aurangabad, India. Capmul MCM C8 was received from Abitec Corporation. Tween-80, PEG-400, Aerosil 200, Avicel pH 101 were purchased from the Loba Chemie pvt Ltd. All other chemicals used in the present research were of analytical grade.
polylethylene glycol 400 was selected based on ternary phase diagram which was used for the preparation of SNEDDS. The mixture of drug with oil and S-mix was taken in the vial, sealed and placed in water bath to at 40-50 °C temperature to help in homogenization. It was further mixed by vortex to obtain uniform mixture and cooled at 25-30 °C and stored at same temperature [10], [11]. This formulation was kept under visual observation to examine signs of turbidity or phase separation. The various batches were designed as given in Table 1.

**TABLE 1: COMPOSITION OF DESIGNED FORMULATION**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide (mg)</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Capmul C8</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Tween 80</td>
<td>4.5</td>
<td>2.3</td>
<td>1.75</td>
<td>1.4</td>
<td>4.67</td>
<td>5.25</td>
<td>5.56</td>
<td>4.5</td>
</tr>
<tr>
<td>PEG 400</td>
<td>4.5</td>
<td>4.67</td>
<td>5.25</td>
<td>5.56</td>
<td>2.33</td>
<td>1.75</td>
<td>1.4</td>
<td>4.5</td>
</tr>
<tr>
<td>Total (ml)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

2.4 Evaluation of liquid SNEDDS

Microscopy
Microscopic study was conducted on the developed formulation to identify probable changes which might have occurred during its storage at normal condition at (25-30 °C). The various parameters evaluated were homogeneity, color, transparency, and phase separation.

Self Emulsification Time Analysis
Self-emulsification time of SNEDDS was estimated by USP type II dissolution apparatus. The formulation (500 mg) was added gradually into 500 ml distilled water maintained at 37+0.5 °C and at 50 rpm. Emulsification time was assessed visually.

Determination of Cloud Point
Cloud point measurement is an essential parameter to form a stable formulation. It was determined by addition of distilled water to formulation in water bath maintained at 60 °C. The time required for solution to become opaque and cloudy was noted as the cloud point.

Particle Size Measurement and Polydispersity Index
The mean particle size distribution and the polydispersity index of the selected liquid SNEDDS formulation was determined by particle size analyzer instrument.

Zeta Potential
The Zeta potential of the selected liquid SNEDDS formulation were performed by Zetasizer instrument.

Dilution test
The dilution test was performed by diluting all formulations 100 and 1000 times with dissolution media like 0.1 N HCL, phosphate buffer (pH 6.8) and water. The diluted SNEDDS were stored for 24 hr and monitored for any signs of phase separation or drug precipitation [12], [13].

Drug Stability

**Temperature stability**

SNEDDS of Budesonide was kept under ambient conditions (20-25 °C) for 3 months and observed for changes in physical stability. The stored sample was evaluated each month for the appearance, color, and drug content.

Centrifugation stability
The liquid SNEDDS preparation (100 mg in 100 ml water) was subjected to centrifugation (5000 rpm for 30 m) and changes in homogeneity of nano emulsion were observed.

Preparation of solid SNEDDS
The liquid SNEDDS was transformed into solid by adding different adsorbent blend in fixed ratio like mixture of Avicel PH 101 and Aerosil 200 (1:1 and 1:2), and mixture of Avicel 101 and anhydrous dibasic calcium phosphate (1:2 and 1:2) for a period of 10 min while gently stirring with magnetic stirrer. The resulting product was dried in oven at 40 °C for 48 hrs to obtain dried SNEDDS [14].

Evaluation of solid SNEDDS

Determination of drug content
The solid SNEDDS sample (100 mg) was dissolved in 10 ml methanol and stirred by vortex mixing, followed by membrane filtration technique using 0.45 µm filter. The concentration of was drug estimated by UV spectroscopy using methanol as solvent at 247 nm. The solid SNEDDS was evaluated for micromeritic properties such as bulk density, tapped density, angle of repose, Carr’s index and Hausner’s ratio.

Preparation of Budesonide coated tablet containing solid SNEDDS
The core tablets were prepared containing solid SNEDDS by direct compression method using different excipient like Lactose as diluents, magnesium stearate as a lubricant, Sodium starch glycolate as a superdisintegrant and Talc as an antiadherant. The tablets were coated with pH sensitive polymer Eudragit S 100 in pan coater. The 10 % polymer solution was prepared in 5 ml each of acetone and isopropyl alcohol. The percent weight gain was validated to 5% .

In vitro dissolution of coated tablets
The coated tablets of budesonide were subjected to drug release using pH 1.2 HCL buffer, phosphate buffer pH 6.4, 6.8 and 7.4 buffer as dissolution medium. The USP type II apparatus was used to perform dissolution at 37±0.5 °C and 50 RPM. The fixed quantity of sample was withdrawn at 1 hr interval for the period of 12 hr and drug release was determined.

3 RESULTS AND DISCUSSION

3.1 Construction of pseudoternary phase diagram
The stability of the formulation depends on the final ratio of the selected components. The ratio of components (oil:surfactant:cosurfactant) was optimized using ternary phase diagram. The result indicated S-mix:oil ratio of 3:7 exhibited greater stability. Figure 1 shows the ternary phase diagram in which dark region shows formation of nanoemulsion. It was clear that, 3:7 ratio of S-mix and oil shows greater nanoemulsion area hence it was selected for further study.
3.2 Preparation and evaluation of liquid SNEDDS

The prepared liquid SNEDDS formulations were evaluated for different parameters as given in Table 2.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Transparency</th>
<th>Phase separation</th>
<th>Centrifugation study</th>
<th>Self emulsification time analysis (min)</th>
<th>Robustness of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Transparent</td>
<td>Observed</td>
<td>No change</td>
<td>1.25 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F2</td>
<td>Transparent</td>
<td>Not observed</td>
<td>No change</td>
<td>2.22 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F3</td>
<td>Transparent</td>
<td>Not observed</td>
<td>No change</td>
<td>2.40 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F4</td>
<td>Transparent</td>
<td>Not observed</td>
<td>No change</td>
<td>1.55 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F5</td>
<td>Transparent</td>
<td>Observed</td>
<td>No change</td>
<td>1.15 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F6</td>
<td>Transparent</td>
<td>Not observed</td>
<td>No change</td>
<td>1.00 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F7</td>
<td>Transparent</td>
<td>Not Observed</td>
<td>No change</td>
<td>0.56 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F8</td>
<td>Transparent</td>
<td>Not Observed</td>
<td>No change</td>
<td>1.10 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
<tr>
<td>F9</td>
<td>Transparent</td>
<td>Not Observed</td>
<td>No change</td>
<td>1.20 Turbidity or phase separation not observed</td>
<td>Turbidity or phase separation not observed</td>
</tr>
</tbody>
</table>

The zeta potential of the F7 formulation was determined and observed -5.43 mV indicating the stability of the formulation. The presence of negative charge on the droplets will result in the repulsion and greater stability. (Figure 3)

3.3 Stability study

The stability of the formulation was assessed against temperature and centrifugation. It was clear that, formulation was stable at the study temperature and centrifugation conditions. There was no phase separation or flocculation at the selected conditions of stability showing the stability of the formulation F7.

3.4 Preparation and evaluation of solid SNEDDS

The liquid SNEDDS was converted to solid by adding the adsorbents in different ratio and by drying in oven. The resulting solid SNEDDS product was evaluated for drug content and micromeritic properties. The micromertic properties are given in Table 3. It can be seen that, formulation exhibited good flow properties as clear from the lower values of flow indicators. The good flow properties may be due to change in particle size and shape. In addition, drug content was found 99.37% [15].

All the formulations were found transparent and stable to centrifugation. The dilution test indicated no phase separation except in F1 and F5 formulation. Moreover, increase in the concentration of surfactant decrease the self emulsification time and increases its stability. The formulation F7 showed less self emulsification time than other hence it was selected as optimized and further evaluated. The cloud point is the temperature above which turbidity appears in the system. The cloud point was determined for optimized F7 formulation and was obtained above 60 °C. Also, this formulation was subjected to particle size analysis and the result is presented in figure 2. The droplet size of F7 formulation was found 247.6 nm and uniform distribution was seen. The uniformity of droplet size was also confirmed form the lower value of polydispersity index (0.155).
3.5 Preparation and evaluation of coated tablet

The core tablets of the solid SNEDDS were prepared by direct compression method and coated with pH sensitive polymer eudragit S-100 with weight gain of 5%. The resulting tablets were evaluated for shape, diameter and thickness. The tablets were round having diameter of 12.2 mm and thickness 5.4 mm.

3.6 In vitro dissolution of coated tablets

Dissolution study is an important quality control tool for the performance of the drug product in vivo. The study was conducted in different dissolution media like 0.1 N HCl, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer. The percent drug release is presented in figure 4. The tablet remained intact for 5 hrs in 0.1 N HCl and pH 6.8 phosphate buffer. The drug release was started after tablet comes in contact with pH 7.4 phosphate buffer. Moreover, the cumulative drug release at the 12 hrs was 98.11±2.68 %. This enhanced drug release was due to improved solubility through SNEDDS.

![Figure 4: Percent drug release from coated tablet formulation](image)

4 CONCLUSION

The SNEDDS of the budesonide was formulated and incorporated in colon targeted drug delivery system successfully. The pH sensitive polymer coated tablets containing solid SNEDDS did not showed drug release for 5 hrs and greater than 95% cumulative drug release at 12 hrs. Moreover, the drug content of the tablet was also found 99.37%. Hence, colon targeted tablets of budesonide were prepared and evaluated by incorporating the SNEDDS.

ACKNOWLEDGMENT

Authors are thankful to Principal, Amrutvahini College of Pharmacy, Sangamner, for providing necessary facilities to carry out this research.

REFERENCES


