FORMULATION AND IN-VITRO EVALUATION OF GLIBENCLAMIDE DRY EMULSION IN VEGETARIAN CAPSULES

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Abstract:
The purpose of this study is to improve the bioavailability and dissolution of Glibenclamide in the preparation of a dried emulsion. This dry emulsion formulation is filled in HPMC capsules as it is of vegetarian source but not gelatin because of several drawbacks. The animal source of gelatin may be a problem for some consumers, such as vegetarian and religious groups or ethical groups, since unmodified gelatin is subjected to cross linking in contact with aldehydes, solubility problems can be expected with certain fill formulations. Dry emulsions are prepared by the drying of liquid emulsions in which there is a solid form in the aqueous phase. The solid support provides the dry and bulk emulsions. In this preparation the emulsion was dried, sesame oil in which the drug is soluble, hydroxyl propyl methyl cellulose as the organic filler and Tween 80 as the surfactant is used. The dried emulsion was evaluated for the drug content, determination of the globular size and surface characterization, in vitro release of the drug in dry emulsion was studied by a type II USP-type paddle dissolving apparatus. This study revealed that the solid dry emulsion technique proved to be promising and useful for improving dissolution.

Key Words: Glibenclamide, Dry Emulsion, HPMC capsules, Sesame oil

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INTRODUCTION:
The formulation of the dry emulsion is intended to improve the bioavailability [1, 2] of the drug substances and to reduce their side effects. Dry emulsions are attractive because they are physically and microbiologically stable formulations. They represent a potential system for the administration of oral medicines for lipophilic and sparingly soluble pharmacological substances. The dry emulsions [3] are prepared by techniques such as freeze drying, spray drying and rotary evaporation. For the preparation of dry emulsions, the organic fillers used are lactose, mannitol and malto-dextrin. Co-solvents commonly used are polyethylene glycol, propylene glycol, glycerol, and the like. The thickeners used are natural and synthetic gums, cellulose derivatives and colloidal silica. The sweetening agents used are glucose, aspartame, sucrose and the like. For the preparation of oil-in-water emulsions, medium-chain triglycerides are generally used as the lipid phase, the preferred oils being sesame oil [4], olive oil and peppermint oil. Glibenclamide [5] is a second generation sulphonylurea anti diabetic agent with very low solubility in biological fluids. Therefore, in order to improve the bioavailability and stability of the drug, it is formulated as a dry emulsion.

MATERIALS AND METHODS:
Materials: Glibenclamide was obtained as a gift sample from Hetero Drugs Pvt. Ltd. (Hyderabad, India). The sesame oil came from the Empire Scientific Company. Polyethylene glycol was donated by SD fine chemicals; Tween 80 and Span 80 were donated by Gattefosse (Mumbai, India). HPMC K4M obtained from Ontop Pharmaceuticals. HPMC capsules were administered by natural and synthetic gums, cellulose derivatives and vegetable polysaccharides or subsidiaries thereof, for example, carrageenans or changed types of starch and cellulose. Regardless of the considerable favourable circumstances of gelatin containers, gelatin has a few disadvantages that breaking points its utilization for cases. The animal source of gelatin may be a problem for some consumers, such as vegetarian and religious groups or ethical groups, since unmodified gelatin is for some consumers, such as vegetarian and religious groups or ethical groups, since unmodified gelatin is cross linked upon contact with aldehydes, solubility problems may be encountered with certain formulations filling. Vegetarian capsules [7] consist of starch, HPMC, PVA and alginate.

Preparation of the solution for the calibration curve: Solutions of 2 to 10 μg / ml were prepared from the standard working solution (100 μg / ml) and the calibration curve was plotted at concentrations of 2, 4, 6, 8 and 10 μg / ml. The standard calibration curve of Glibenclamide in 0.1 N HCl at 339.6 nm was plotted taking absorbance on the Y-axis and concentration on the X-axis and following the beer’s law.

Pre-formulation Studies:
Studies of compatibility with excipients: Before formulating the pharmaceutical substances in dosage form, it is essential that they are chemically and physically characterized [11, 12]. The preformulation studies provide the information necessary to define the nature of the drug substance and provide a framework for the combination of drugs with pharmaceutical excipients in the manufacture of a dosage form. In this compatibility study, one of the requirements for the selection of polymers or vehicles suitable for the pharmaceutical formulation is their compatibility.

FTIR studies: FTIR studies were carried out using the potassium bromide pellet method.

Melting point determination: The melting point of the Glibenclamide was determined by capillary method.

Solubility: The solubility of Glibenclamide was determined by adding the excess amount of drug but measured in a 100 ml volumetric flask containing 0.1 N HCl and maintained under stirred conditions at 370 °C ± 0.5 in a stirrer water bath for 2 hours. The dispersions were filtered on Whatmann filter paper and analyzed for the amount of dissolved drug.

Glibenclamide pure drug analysis: The absorbance of the prepared solutions was checked using a UV spectrophotometer at 339.6 nm. 0.1N HCl was used as the blank.

Evaluation Studies [13-15] for the Formulated Dry Emulsion:
Dry emulsion is subjected to the following evaluation tests.

Drug entrapment:
The drug entrapment of the prepared dry emulsion should be in the range of 98.772 to 101% w/w.

In-vitro dissolution studies [16, 17]:
In vitro drug release studies from dry emulsions were performed using a USP type 2 dissolution apparatus (paddled apparatus) at 25 rpm. A dry emulsion preparation equivalent to 5 mg of Glibenclamide was taken. The dissolution medium consisted of 900 ml of distilled water maintained at 37 ± 0.5 °C. At predetermined time intervals 5 ml of aliquot were removed and an equivalent volume of fresh solution medium was immediately added. The amount of drug released was estimated by measuring the absorbance at 339.6 nm using a spectrophotometer. A cumulative percentage of drug release was observed over a time interval of five minutes. The dissolution profiles of the pure drug and dry emulsion were compared on the basis of the time required to release the maximum drug.

Particle size analysis:
The particle sizes of the charged formulations were measured using an optical microscope equipped with an ocular micrometer and on stage and the particle size distribution was calculated. For this, the Olympus model (SZX-12) was used with a resolution of 30 x. The instrument was calibrated in an eyepiece unit. The micrometer was equal to 1/30 mm (33.33 μm). In all measurements, at least 100 particles were examined in five different domains.
Each experiment was carried out in triplicate. The dried emulsions were diluted to 100 ml with distilled water. The droplet size distributions and the polydispersibility index of the resulting dry emulsions were determined using a particle size analyzer.

Globule size determination [18]: Microscopic examination of the emulsion was observed before and after reconstitution, the minimum size of the oil globule in the micron range is important since the reduction of the surface leads to an improvement in the solubility and dissolution rate of an emulsion.

Estimation of drug content: The percentage of the drug content of the dry emulsion formulations was estimated by dissolving the appropriate amount of dry emulsion equivalent to 100 mg in water. The samples were thoroughly mixed to dissolve the drug in water. The samples were sonicated by ultrasound for 15 minutes and analyzed using a UV spectrophotometer and recorded absorbance.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glibenclamide</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg</td>
<td>5mg</td>
</tr>
<tr>
<td>Sesame oil</td>
<td>100mg</td>
<td>200mg</td>
<td>100mg</td>
<td>300mg</td>
</tr>
<tr>
<td>Tween 80</td>
<td>720mg</td>
<td>640mg</td>
<td>-</td>
<td>200mg</td>
</tr>
<tr>
<td>Span 80</td>
<td>-</td>
<td>-</td>
<td>180mg</td>
<td>500mg</td>
</tr>
<tr>
<td>PEG-400</td>
<td>180mg</td>
<td>160mg</td>
<td>720mg</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>2g</td>
<td>2g</td>
<td>2g</td>
<td>2g</td>
</tr>
<tr>
<td>Purified water</td>
<td>Up to 10ml</td>
<td>Up to 10ml</td>
<td>Up to 10ml</td>
<td>Up to 10ml</td>
</tr>
</tbody>
</table>

Table 1: Formulation Table with selected excipients

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Drug content</th>
<th>Drug entrapment efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>95.93±0.611</td>
<td>95.04±0.311</td>
</tr>
<tr>
<td>F2</td>
<td>97.47±0.351</td>
<td>98.83±0.314</td>
</tr>
<tr>
<td>F3</td>
<td>72.96±0.568</td>
<td>70.33±0.709</td>
</tr>
<tr>
<td>F4</td>
<td>68.62±0.655</td>
<td>64.93±0.450</td>
</tr>
</tbody>
</table>

Table 2: Drug Content and Drug Entrapment Efficiency Data of Dry emulsions

All values are expressed as mean ± standard deviation, (n=3)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Range in micron</th>
<th>No. of Globules Before Reconstitution</th>
<th>No. of Globules After Reconstitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Globule Size Distribution of Dry Emulsion before and after Reconstitution

<table>
<thead>
<tr>
<th>Time</th>
<th>Cumulative % release of pure drug and formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>pure drug</td>
<td>F1</td>
</tr>
<tr>
<td>5</td>
<td>11.412</td>
</tr>
<tr>
<td>10</td>
<td>13.868</td>
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<tr>
<td>15</td>
<td>15.226</td>
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<td>30</td>
<td>16.07</td>
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<td>45</td>
<td>17.112</td>
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<tr>
<td>60</td>
<td>19.064</td>
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<tr>
<td>75</td>
<td>20.216</td>
</tr>
<tr>
<td>90</td>
<td>20.404</td>
</tr>
</tbody>
</table>

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RESULTS AND DISCUSSION:

Melting point determination:
The melting point of the Glibenclamide was determined by the capillary method. The melting point was 172 °C.

Evaluation Studies for the Dry Emulsion formulation:
The formulated Dry emulsion was subjected to the following evaluation tests.

1. Drug Entrapment Efficiency:
The drug entrapment of the prepared dry emulsions was found to be in the range of 95.04-98.831 and the values are shown in the Table 2.

2. Globule size determination:
The size distribution of the globules was analyzed and calculated. Prior to reconstitution, it suggests that the globule size has been reduced, which contributes to the high dissolution rate of the dry emulsion and subsequent reconstitution suggests that the size of the globules remains almost identical, and also suggests the stability of the emulsion, after reconstitution.

3. Drug Content Estimation:
The drug content for the prepared formulations F1, F2, F3 and F4 was found to be 95.933, 97.473, 72.966 and 68.62% respectively.

In-vitro Drug release studies:
From in vitro drug release profile it was found that the % drug release from dry emulsions in HPMC capsules was higher than that of pure drug. The cumulative % drug release for formulations F1, F2, F3 and F4 at the end of 90 min was 59.378, 68.416, 29.287 and 33.291% respectively, where as pure drug showed 20.404% drug release in 90 minutes. At the end of 90 min, formulation F2 showed maximum
cumulative % drug release of 68.416%. Stability studies were conducted for a period of 3 months. The cumulative % drug release for formulations and pure drug at the end of 90 min was shown in Table 4.

CONCLUSION:
By formulating Glibenclamide in the form of a dry emulsion, its solubility and dissolution rate have been improved. The dry emulsion formulation was analyzed for stability studies [19, 20] for 3 months at 45 °C with 75 ± 5% RH. The emulsion was analyzed by drug trapping and cumulative % drug release over a 3-months period without variation in results. After three months, the dry emulsion was reconstituted and the emulsion formed was stable with the desired consistency and viscosity and without any sign of instability. Compared to the dissolution rate of the Glibenclamide formulations, it was found that pure Glibenclamide - Dry Emulsion. From the previous study, it can be concluded that the dry emulsion formulation (F2) showed immediate release of the drug relative to pure Glibenclamide.

REFERENCES: