Effect of Polyethylene glycol 4000 (PEG4000) Solution on the in Vitro Release Profile of Nifedipine from Polymer Matrices

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The effect of PEG4000 solution on the in vitro release of nifedipine, a calcium entry blocker and a poorly water soluble drug was evaluated. Nifedipine tablets containing 10 mg of nifedipine, 20% of one of four polymers—Eudragit L-100 and Rs, ethylcellulose and carbopol 941, 2% lubritab and an adequate quantity of Encompress to yield 300 mg weight tablets—were formulated using the direct compression method. Tablets were compressed to a hardness of 5N, and an in vitro dissolution profile was performed on the tablets in 70% ethanol and in ethanolic PEG4000 solutions.

The results obtained indicated enhancement of nifedipine release from two of the polymer matrices (Eudragit L-100 and ethylcellulose) in the presence of PEG4000 and a retardant effect from carbopol 941 matrix. It is suggested that carbopols may not be suitable for use in the formulation of nifedipine tablets since there are some physiological surfactants present in the gastrointestinal tract (GIT).

Key words nifedipine; polymer matrices; surfactant; dissolution profile

The availability of nifedipine, a calcium entry blocker from oral and rectal dosage forms has been reported to be about 40—60%.1 This is said to be due to the pre-systemic metabolism.2 The absorption of nifedipine when administered in oral dosage forms is reportedly inferior because of its very poor water solubility.3 The dissolution of nifedipine compacts is enhanced in the presence of surfactants and some polymers.3 Its absorption from the gastrointestinal tract (GIT) is thought to be aided by some physiological surfactants which have been confirmed to be present in the GIT.4 The incorporation of surfactants in tablets was reported to improve disintegration,5 while the addition of surfactants to the dissolution medium increased the dissolution of powder drugs and their tablets.6,7

In this study we evaluated the effect of solutions of PEG4000 on the in vitro release of nifedipine from four polymer matrices. The four polymers chosen (Eudragit L-100, Eudragit Rs, ethylcellulose and carbopol 941) possess varying sustained release matrix capacities. Nifedipine was selected since this drug exhibits all the required pharmacokinetic and physico-chemical properties which make it a good candidate for incorporation in a sustained release formulation.

MATERIALS AND METHODS

The following materials were used as procured from their manufacturers without further purification—carbopol 941 (B.F. Goodrich Chem. Co., Ohio), Eudragit L-100 and Rs (Reohm GmbH, Germany), ethylcellulose mPc (Fluka), lubritab (Capitol City Prod., U.S.A.), nifedipine, a generous gift from Bayer Pharmaceutical Company, Germany, PEG4000 (BDH LAB. Poole, U.K.), and Encompress (Edward Mandel Co., U.S.A.).

Preparation of Nifedipine Tablets Each nifedipine tablet contained 10 mg of nifedipine, 20% of either carbopol 941 or Eudragit L-100 or Rs or ethylcellulose, 2% lubritab and enough Encompress to yield tablets 300 mg in weight. Weighed quantities of the materials excluding lubritab to yield 100 tablets per batch were mixed by geometric dilution method in a specimen bottle for 10 min. Weighed quantity of lubritab was added and the powder mixture was mixed for another 5 min. The powder mixture was directly compressed into tablets in an F-3 Manesty single punch tabletting machine fitted with 9.5 mm biconcave punches. The targeted weight of each tablet was 300 ± 5 mg. Tablets were compressed to a hardness of 5N. Compression was carried out under subdued sunlight.

In Vitro Dissolution Studies The magnetic stirrer-hot plate method was adopted and the dissolution medium consisted of 300 ml of freshly prepared 70% (v/v) ethanol maintained at 37 ± 1°C. One tablet from each batch was placed in a basket (425 μm aperture) immersed in the dissolution medium. The stirrer was operated at a speed of 50 ± 1 rpm by switching on a hot plate and adjusting a speed controller. Samples (5 ml) were withdrawn at 30 min intervals for an 8 h period. Withdrawn samples were analysed spectrophotometrically at 338 nm using spectronic 20. The percentages of nifedipine released were determined from a calibration curve previously determined for nifedipine. The above procedures were repeated for nifedipine tablets using dissolution medium that consisted of 0.5 or 1.0% (w/v) of PEG4000. Nifedipine is very light sensitive8,9 and all dissolution studies were conducted under subdued light. The beaker containing the dissolution medium was partially sealed to reduce evaporation of the dissolution medium as much as possible.

RESULTS AND DISCUSSION

The tablets were found to be smooth, glossy and light yellow in colour. They exhibited less than 0.05% friability and were non-disintegrating.

The dissolution profile of nifedipine from 20% (w/w) of the polymer matrices is shown in Fig 1. The blockter's release profile was analysed using the concept of $T_{25}$ and $T_{50}$. These represent the time taken for 25 and 50%
Table 1. $T_{25}$ and $T_{50}$ Values of Nifedipine Tablets

<table>
<thead>
<tr>
<th>No surfactant</th>
<th>$T_{25}$ (min)</th>
<th>$T_{50}$ (min)</th>
<th>Surfactant (%)</th>
<th>$T_{25}$ (min)</th>
<th>$T_{50}$ (min)</th>
<th>$T_{25}$ (min)</th>
<th>$T_{50}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit Rs</td>
<td>65</td>
<td>195</td>
<td>0.5</td>
<td>11</td>
<td>165</td>
<td>18</td>
<td>265</td>
</tr>
<tr>
<td>Eudragit L-100</td>
<td>150</td>
<td>360</td>
<td>1.0</td>
<td>15</td>
<td>150</td>
<td>9</td>
<td>135</td>
</tr>
<tr>
<td>Carbopol 941</td>
<td>97.5</td>
<td>—</td>
<td></td>
<td>70</td>
<td>190</td>
<td>69</td>
<td>110</td>
</tr>
<tr>
<td>Ethylecellulose</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Fig. 1. Release Profile of Nifedipine from the Polymer Matrices
Dissolution medium: 70% (v/v) ethanol. —■—, Eudragit L-100; — ▴—, Eudragit Rs; — △—, Ethylecellulose; — □—, Carbopol 941.

of the drug to be released, respectively. From Table 1, the fastest release of nifedipine occurred from Eudragit Rs matrix within the first 30 min, while the slowest release was from carbopol 941 matrix within the same period. A similar trend occurred at 50% drug release. Ethylecellulose exerted the greatest retarding effect on nifedipine release after 4 h followed by carbopol 941, Eudragit L-100 and Rs in that order. Figures 2 and 3 show the release profile of nifedipine in the presence of 0.5 and 1.0% (w/v) of PEG 4000. Enhancement of nifedipine release was seen from tablets containing either Eudragit L-100 or ethylecellulose, within the first 2 h of drug release, an effect which increased slightly with increase in the concentration of PEG4000. There was a slight decrease in the amount of nifedipine released from Eudragit Rs matrix. Slower release of the drug occurred from this polymer matrix as the concentration of PEG4000 was increased from 0.5 to 1.0% (w/v). There was a marked retardant effect of nifedipine release from carbopol 941 matrix in the presence of PEG4000, an effect which increased with greater concentration of PEG4000.

The high retardant effect of ethylecellulose in 70% (v/v) ethanol could be attributed to the fact that it requires polar liquids as solvent, in which dipole interactions or hydrogen bonding between polymer and solvent molecules take place. Solvation does not, however, necessarily lead to solution because the liquid, if it is to act as a solvent, must dissolve the solvated polymer. This process can be very slow because of high viscosity of the solvated polymer, a process which is capable of retarding drug release. Eudragit L-100 and Rs are enteric acrylic resins which are soluble in solvents from pH 6. The pH of 70% (v/v) ethanol approximates this value, hence an enhanced release of the drug is expected from these polymer matrices. Carbopol 941, on the other hand, exhibits maximum viscosity at pH range of 5 to 10.11 The polymer is ex-
pected to exert high viscosity in 70% (v/v) ethanol, a process which may reduce the release of drug depending on the nature of the polymer. The mode of drug release from polymers depends to some extent on the nature of the polymer. For instance, ethylcellulose and Eudragits being hydrophobic in nature are thought to release their drug content by leaching, while hydrophilic polymers such as carbopol release their drug content primarily by diffusion or by zero order.

The presence of surfactants in the dissolution medium has been shown to enhance the solubility of nifedipine powder. Surfactants may enhance the dissolution process of a poorly soluble drug in a tablet by a reduction of interfacial tension and micelle formation. At a critical micelle concentration, the surfactants form micelles which arise from the aggregation of molecules containing distinct regions of hydrophilic and lipophilic characters and which trap the drug molecules, thereby apparently increasing solubility. As a result, enhancement of nifedipine release from the four polymer matrices should be expected. However, a reverse and profound retardant effect occurred with carbopol 941. Carbopol has the ability to form cross-linked systems termed gels. Gelation enhances the rate of release of drugs from dosage forms. The characteristic feature of a gel system is the considerable increase in viscosity above the gel point. The presence of PEG4000 may have affected the process of gelation in carbopol 941 and hence the relatively slow release rate observed.

CONCLUSION

From the results obtained in this study, there is the indication that the Eudragit L-100 and ethylcellulose would be best suited for the formulation of nifedipine tablets intended for sustained action. Carbopol may not be suitable for the formulation of nifedipine tablets since its drug release in the GIT is likely to be extensively retarded in the presence of some physiological surfactants which are known to be present in the GIT.

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