Development of Extended Release Coevaporates and Coprecipitates of Promethazine HCl with Acrylic Polymers: Formulation Considerations

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The present investigation studied a novel extended release system of promethazine hydrochloride (PHC) with acrylic polymers Eudragit RLPO and Eudragit RS100 in different weight ratios (1:1 and 1:5) using coevaporation and coprecipitation techniques. Solid dispersions were characterized by Fourier-transformed infrared spectroscopy (FT-IR), Differential scanning calorimetry (DSC), Powder X-ray diffractometry (PXRD), Nuclear magnetic resonance (NMR), Scanning electron microscopy (SEM) as well as solubility and in vitro dissolution studies in 0.1 N HCl (pH 1.2), double distilled water and phosphate buffer (pH 7.4). Adsorption test from drug solution to solid polymers were also performed. Selected solid dispersion system was subjected to direct compression and compressed tablets were evaluated for in vitro dissolution studies. The progressive disappearance of peak in thermotrophic profiles of coevaporates were related to increasing amount of polymers while SEM studies suggested homogenous dispersion of drug in polymer. Eudragit RLPO had a greater adsorptive capacity than Eudragit RS100 and thus its coevaporates in 1:5 ratio exhibited higher dissolution rate with 91.90% drug release for 12 h. Among different formulations, tablets prepared by Eudragit RLPO coevaporates (1:5) displayed extended release of drug for 12 h with 90.87% release followed by zero order kinetics ($r^2=0.9808$).

Key words: promethazine hydrochloride; Eudragit RLPO; solid dispersion; Eudragit RS100; coevaporate; coprecipitate

The solid dispersion approach is commonly used to improve the dissolution properties of poorly water soluble drugs using hydrophilic polymeric carriers as dispersing agents. More recently, several studies on solid dispersions have been carried out using water insoluble carriers to produce sustained release pharmaceutical forms of freely water soluble drugs.1–3) For this goal, different types of polymethacrylates (Eudragit) have been considered. The most interesting among acrylic polymers are highly permeable Eudragit RL and low permeable Eudragit RS, both are neutral copolymers of poly (ethylacrylate, methyl methacrylate) and trimethyl aminoethyl methacrylate chloride and are insoluble in water and digestive juices, but both swell and are permeable. Extended release systems are the methods that can achieve therapeutically effective concentrations of drug in systemic circulation over an extended period of time. Hasegawa et al.4–8) and Fujii et al.9–13) used the solid dispersion method for this purpose. A combination of solid dispersion and extended release is one of the attractive approaches since supersaturation of the drugs can be achieved by employing solid dispersion technique.14) In present study, Eudragit RLPO and Eudragit RS100 have been used as retardants to prepare a novel extended release system of highly water soluble medicine promethazine hydrochloride using coevaporation and coprecipitation techniques in order to extend their dissolution rates. Selected solid dispersion system was further subjected to tablet preparation by direct compression to study the feasibility of incorporating solid dispersion to be formulated as drug delivery system.

Experimental

Materials

Promethazine hydrochloride (PHC) was supplied by Seimens Laboratory, India. Eudragit RS100 (RS100) and Eudragit RLPO (RLPO) were gifted by Rohm Pharma, Germany. Microcrystalline cellulose (Avicel PH101) was obtained from Fluka, India. Hydrogenated soybean oil (Sterotex HM) and Silicon dioxide were kindly gifted from Merck India Limited, Mumbai. Other chemicals were of analytical grade. Double distilled water was used throughout the studies.

Preparation of Solid Dispersions

PHC and polymers Eudragit RS100 (RS) and Eudragit RLPO (RL) were dissolved in methanol in 1:1 and 1:5 drug: polymer weight ratios. The methanolic solution was evaporated at 40°C and dried in vacuum desiccator. The solid mass was grounded and sifted (150 µm sieve) to get coevaporates (CPs).15) Physical mixtures (PMs) with corresponding weight ratios were prepared by triturating the drug and polymer in a glass mortar. The powders were then sifted (150 µm sieve) and stored in desiccator. The solid dispersion was assigned single formulation code comprising of method of preparation, weight ratio and type of polymer used. PM1RS, CE1RS, CP1RS are physical mixture, coevaporate and coprecipitate prepared with RS100 in 1:1 weight ratio whereas PM5RS, CE5RS and CP5RS are physical mixtures, coevaporate and coprecipitate prepared with RS100 in 1:5 weight ratios. Similarly, PM1RL, CE1RL and CP1RL are physical mixture, coevaporate and coprecipitate prepared with RLPO in 1:1 weight ratio while PM5RL, CE5RL and CP5RL are physical mixtures, coevaporate and coprecipitate prepared with RLPO in 1:5 weight ratios.

Determination of Drug Content

Ten milligrams of each of the solid dispersion was accurately weighed and diluted up to 10 ml with double distilled water. From this, 1 ml of sample was withdrawn and diluted up to 10 ml with double distilled water and assayed spectrophotometrically for promethazine HCl at 249 nm using spectrophotometer curve in double distilled water. The studies were conducted in triplicate.

Solubility Measurements and Adsorption Studies

Solubility of solid dispersions was studied in 0.1 N HCl (pH 1.2), double distilled water and phosphate buffer (pH 7.4). The samples were subsequently allowed to equilibrate at 37±0.1°C in mechanical shaker (HICON, India) for 24 h. The samples were filtered, suitably diluted and assayed spectrophotometrically (Shimadzu, Japan).16) For adsorption studies, the drug was dissolved in phosphate buffer pH 7.4 (50 ml). A 10 fold weight of grounded RS100 or RLPO was added to the solution, and the mixture was magnetically stirred at room temperature for 15 d. Samples were periodically drawn, filtered, diluted and assayed spectrophotometrically (Shimadzu, Pharmaspec 1700, Japan) at 249 nm.17)

Preparation of Tablets

Seventy-five milligrams of PHC or CE or PM equivalent to 75 mg along with 56% lactose, 28% Avicel PH 101 and 1% Sterotex HM were blended in double cone blender (HICON, India). The powder blends were compressed by direct compression method using electrically operated single punch tablet machine (10 mm die diameter, Jindal Scientific Industries Pvt. Ltd., India) to get 500 mg tablets.

Observation of Dissolution Behavior of PHC from Solid Dispersions and Tablets

The dissolution behavior of PHC from pure PHC powder or

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its CEs, CPs and PMs was performed using USP XXVII Apparatus I in 900 ml of 0.1 N HCl (pH 1.2), double distilled water, and phosphate buffer (pH 7.4) at an agitation rate of 100 rpm. The temperature of medium was maintained at 37 ± 0.5 °C. Seventy-five milligrams of drug or its equivalent of the prepared dispersions were packed in transparent gelatin capsules and analyzed for dissolution. Tablets prepared with selected CE, its corresponding PM and PHC were also analyzed for dissolution. A 5.0 ml sample was withdrawn at specific time points over a 12 h period and replaced immediately with equal volume of fresh dissolution medium to maintain a constant volume. The aliquot samples were filtered and the drug concentrations were determined spectrophotometrically at 249 nm. Drug release kinetics was investigated by fitting the dissolution data to PCP Disso V 2.0 software, Pune, India.

Analysis of State of Solid Dispersions

The solid state of prepared CEs, CPs and PMs was analyzed by differential scanning calorimetry (PERKIN ELMER DSC-7), powder X-ray diffraction with diffractometer (PW 3040/60 X’PERT PRO, Netherlands), infrared spectroscopy with FT-IR spectrophotometer (SHIMADZU 8201 PC), scanning electron microscopy (LEO 435 VP, UK) and 1H-NMR (Bruker Avance 400, Japan).

Results and Discussion

Determination of Drug Content

The actual drug content of solid dispersion systems were estimated in the range of 13.06 ± 0.001% to 47.98 ± 0.001% (Table 1). The drug content was found to be uniform in all solid dispersions and was in good agreement with theoretical drug content.

Solubility Measurements and Adsorption Studies

The solubility of PHC in 0.1 N HCl (pH 1.2), double distilled water and phosphate buffer (pH 7.4) was found to be 590.0 mg/ml, 557.7 mg/ml and 554.3 mg/ml respectively. The results revealed that the magnitude of drug’s aqueous solubility can be decreased using methacrylate copolymers (Fig. 1). It was interesting to note that the magnitude of decreased solubility in physical mixtures was quite similar to that of solid dispersions indicating that preparation conditions used to obtain solid dispersions did not ultimately induce polymorphic changes or amorphization of drug molecules. However, increasing the drug: polymer ratio from 1:1 to 1:5 exhibited approximately two fold decrease in magnitude of drug solubility in each medium irrespective of the preparation method. The behavior of physical mixtures thus indicated that a dilution effect of drug microcrystal within the polymer network is mainly responsible for changes observed during solubility studies. Among all solid dispersions, CE5RL had greater capacity to retard the solubility of PHC i.e. 4.57 mg/ml, 4.55 mg/ml and 3.09 mg/ml in 0.1 N HCl (pH 1.2), double distilled water and phosphate buffer (pH 7.4) respectively. The rank order of decrease in solubility was as follows: 0.1 N HCl (pH 1.2) > double distilled water > phosphate buffer (pH 7.4) (Fig. 1), this was because of the fact that PHC possesses a basic group that becomes protonated at acidic pH and makes the drug readily soluble.18) To further evaluate the affinity between the tested molecules and polymers, sorption of drugs onto RS100 and RLPO was calculated quantitatively. The ability of Eudragit polymers to adsorb basic drug from a solution was characterized at pH 7.4. Eudragit RL (Type A) and Eudragit RS (Type B)19) are having different ammonio methacrylate units i.e. 8.85—11.96% and 4.48—6.77% respectively. In adsorption studies RLPO had greater adsorptive capacity than RS100 (Fig. 2), because of its greater number of quaternary ammonium functions, which

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**Table 1. Drug Content and Model Independent Parameters of PHC Solid Dispersions**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulations</th>
<th>Drug contenta (%)</th>
<th>( t_{50%}) (h)</th>
<th>( t_{plateau}) (h)</th>
<th>%DE (0—12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PM1RS</td>
<td>47.98 ± 0.001</td>
<td>1.0</td>
<td>6.0</td>
<td>58.50</td>
</tr>
<tr>
<td>2</td>
<td>CE1RS</td>
<td>45.45 ± 0.001</td>
<td>2.0</td>
<td>4.0</td>
<td>53.85</td>
</tr>
<tr>
<td>3</td>
<td>CPIRS</td>
<td>47.17 ± 0.002</td>
<td>2.0</td>
<td>5.0</td>
<td>30.86</td>
</tr>
<tr>
<td>4</td>
<td>PM5RS</td>
<td>15.56 ± 0.002</td>
<td>3.0</td>
<td>12.0</td>
<td>63.15</td>
</tr>
<tr>
<td>5</td>
<td>CES5RS</td>
<td>13.06 ± 0.001</td>
<td>3.0</td>
<td>9.0</td>
<td>56.43</td>
</tr>
<tr>
<td>6</td>
<td>CPS5RS</td>
<td>13.22 ± 0.001</td>
<td>3.5</td>
<td>6.0</td>
<td>49.08</td>
</tr>
<tr>
<td>7</td>
<td>PM1RL</td>
<td>50.00 ± 0.001</td>
<td>2.0</td>
<td>6.0</td>
<td>63.96</td>
</tr>
<tr>
<td>8</td>
<td>CE1RL</td>
<td>41.73 ± 0.001</td>
<td>2.50</td>
<td>9.0</td>
<td>66.35</td>
</tr>
<tr>
<td>9</td>
<td>CPIRL</td>
<td>47.16 ± 0.002</td>
<td>2.0</td>
<td>7.0</td>
<td>55.44</td>
</tr>
<tr>
<td>10</td>
<td>PMS5RL</td>
<td>15.80 ± 0.002</td>
<td>5.50</td>
<td>12.0</td>
<td>65.22</td>
</tr>
<tr>
<td>11</td>
<td>CES5RL</td>
<td>13.33 ± 0.001</td>
<td>5.75</td>
<td>12.0</td>
<td>74.01</td>
</tr>
<tr>
<td>12</td>
<td>CPS5RL</td>
<td>13.06 ± 0.001</td>
<td>5.50</td>
<td>12.0</td>
<td>59.69</td>
</tr>
</tbody>
</table>

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\(a\) Average of three determinations.
act as the activity sites for electrostatic interactions in solution.

**Effect of Polymer Type and Ratio on Release Mechanism** Figure 3 showed the release profile of PHC from solid dispersions of RS100 and RLPO. The dispersions of drug in polymer matrices strongly influenced their dissolution rate, which appeared slower and more gradual than that of pure drug. At pH 7.4, solid dispersions were found to extend drug release up to 12 h because of decrease in solubility as compared to other media. The presence of the polymer also reduced the massive initial drug dissolution observed with pure PHC. RS100 and RLPO both are insoluble and shows pH independent swelling but RLPO shows high permeability and RS100 shows low permeability to water; hence drug release was relatively retarded with RS100 as compared to freely permeable RLPO. Increasing the drug-to-polymer ratio (from 1 : 1 and 1 : 5) dramatically increased the release time ($t_{50\%}$ values from 1—3.5 h to 2—5.75 h) as well as amount of dissolved drug. However, $t_{50\%}$ values also seemed to be dependent on type of polymer as evidenced by the fact that CE1RS and CE1RL showed $t_{50\%}$ values of 2 h and 2.5 h whereas CE5RS and CE5RL showed $t_{50\%}$ values of 3 h and 5.75 h respectively. This indicated that the polymer properties affected the drug release behavior more prominently when used at higher ratios in the solid dispersions. Another important model independent parameter: dissolution efficiency (DE) defined as the area under the dissolution curve up to a certain time $t$, expressed as the percentage of the area of the rectangle described by 100% dissolution in the same time was also computed. As DE takes into account the entire dissolution profile as a whole, as opposed to $t_{50\%}$ values, this approach employs a more realistic and meaningful method of comparison as well as interpretation of in vitro dissolution data for various formulations. The dissolution efficiency throughout the entire dissolution period ($DE_{0—12h}$) showed that dissolution of the drug from its coevaporates with RLPO was evidently higher than from systems containing RS100 (Table 1). These results might be attributable to the higher swelling and permeation characteristics of RLPO at pH 1.2—7.4. Coprecipitates containing RS100 at higher drug to polymer ratio (CP5RS) was also able to slow down the diffusion rate of drug (Fig. 3). The dissolution data showed that difference in release profiles was mainly influenced by type and amount of polymer used. However, when the type and amount of polymer was similar, the difference in release profile (as in the release pattern of CE5RL and CP5RL) can be better explained based on the different morphological states of drug within the polymer matrix. When PHC was coprecipitated by addition of a nonsolvent, drug–polymer multi dispersion is possible which is characterized by embedding the drug particles within the polymer matrices wherein the exact uniform distribution of the drug within the polymer matrices is difficult with consequent aggregation of drug and polymer in discrete domains resulting in undesirable release profiles. After 12 h of dissolution, none of the solid dispersions prepared with 1 : 1 ratios were able to retard the drug release significantly. However, at 1 : 5 ratio, the CEs displayed more sustained and gradual dissolution as compared to other solid dispersions with RS100 and RLPO. Such a behavior might be due to the fact that the dissolved drug was readsorbed back onto the polymer particles resulting in subsequent saturation of the binding sites on the polymer backbone and evidenced by shorter time to reach plateau ($t_{plateau}$) in the dissolution curves. The phenomenon is proportionally related to the amount of polymer present in solid dispersions.

Table prepared by incorporating coevaporates displayed higher dissolution rate than tablets prepared by physical mixture (Fig. 4). Drug release data revealed that $t_{50\%}$ (4.50 h) and dissolution efficiency up to 12 h (70.23%) is higher in coevaporate tablet (Table 2). The kinetic analysis of the dissolution curves exhibited better fit for the zero order equation with regression value of 0.9912 for coevaporates prepared at 1 : 5 ratio with RLPO and 0.9808 for coevaporate tablets while the data fitted to other mathematical models showed

![Fig. 3. Comparative Dissolution Profiles of PHC and Solid Dispersions in Phosphate Buffer pH 7.4](image1)

![Fig. 4. Comparative Drug Release Profiles of Prepared Tablets of PHC, PM5RL and CE5RL in Phosphate Buffer pH 7.4](image2)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulations</th>
<th>Actual drug content&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$t_{50%}$ (h)</th>
<th>$t_{plateau}$ (h)</th>
<th>%DE&lt;sub&gt;0—12h&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PHC tablet</td>
<td>96.41±0.09</td>
<td>0.25</td>
<td>4.0</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>PM5RL tablet</td>
<td>93.20±0.02</td>
<td>1.50</td>
<td>12.0</td>
<td>61.53</td>
</tr>
<tr>
<td>3</td>
<td>CE5RL tablet</td>
<td>98.82±0.09</td>
<td>4.50</td>
<td>12.0</td>
<td>70.23</td>
</tr>
</tbody>
</table>

<sup>a</sup> Average of three determinations.
poor linearity with experimental data which indicated that drug release from the formulation was independent of the drug concentration.

**State of Solid Dispersions** The physical state of drug in polymer matrices was studied by Fourier-transformed infrared spectroscopy (FT-IR) spectra, powder X-ray diffraction patterns, differential scanning calorimetry (DSC) thermograms and scanning electron microscopy. Physical mixtures with the same composition of solid dispersions were tested as a reference. For PHC, the IR stretching band of tertiary amine around 1020 to 1250 cm\(^{-1}\) (Fig. 5) was still visible in physical mixtures suggesting that there was no interaction between PHC/RLPO in physical mixtures, while it totally disappeared in corresponding coevaporates resulting in a broad band as well as altered stretching and bending vibrations. This result suggested the possibility of intermolecular hydrogen bonding between PHC and RLPO in coevaporates. These interactions were made while the molecules were in solution that is when the distances between the molecules were so small that association between the functional groups is possible. Figure 6 showed PXRD analysis of pure RLPO which was typical of amorphous materials with lack of defined peaks, whereas the pure PHC showed the diffractographic profile of a crystalline material. The systems prepared with lower polymer amounts still showed typical signals of drug crystals, while increasing the RS or RL ratio weakened the intensity of typical signals of drug crystals exerting “diluting” effect on drug signals. DSC run of pure drug exhibited a sharp endothermic peak around 239 °C, corresponding to the melting point (Fig. 7). The dispersion of PHC in RLPO matrix at 1:5 weight ratios resulted in complete suppression of drug fusion peak suggesting possible solid solution of drug in polymer. However, the mere physical dispersion of drug with RLPO also resulted in a modification of the thermotropic profile. The behavior of PHC in physical mixture thus supported the fact that a dilution effect of drug within the polymer network is mainly responsible for the change observed in calorimetric runs of dispersion. FT-NMR (\(^1H\)-NMR) spectrum of PHC (Fig. 8) showed chemical shift of 2.582 ppm (N(CH\(_3\))\(_2\)) while in CE5RL solid dispersion chemical shift was 2.697 to 2.745 ppm (N–(CH\(_3\))\(_2\)) which supported the possible hydrogen bonding between drug and polymer. There seemed to be possible interaction...
between functional groups of drug and polymer due to hydrogen bonding based on FT-IR and FT-NMR but this effect was considered to be a superficial one since the drug kept its chemical structure and potency. However, the issues such as effect of type and concentrations of polymer on matrix structure of solid dispersions were of much significance from the dissolution viewpoint. The physical state of the drug in the polymer matrices as well as electrostatic interaction between drug and ammonium groups present in the polymer backbone contributed to possible saturation of binding sites, consequently leading to modification of release profiles. However, the results again emphasized that low drug to polymer ratio is not sufficient for preparing useful delivery systems since strong interactions between them did not allow a significant release of drug either in acidic or midalkaline dissolution media. SEM studies revealed that in physical mixture, the RLPO existed as individual particles with PHC dispersed in its native crystalline form. Solid dispersion in the same polymer ratio of 1:5 was quite distinct from the physical mixture as it was not possible to identify drug and polymer as separate entities and they seemed to have lost their original crystallographic habits. As opposed to the physical mixture, these particulates displayed much larger, rougher and spherical surfaces, presumably from PHC crystals incorporated into the swelled polymer (Fig. 9).

**Conclusion** The solubility of PHC was markedly decreased after formation of polymeric dispersions. RLPO had greater capacity to adsorb drug as compared to RS100 in phosphate buffer pH 7.4. The analysis by FT-IR, FT-NMR suggested possibility of hydrogen bonding whereas the results of DSC, PXRD and SEM studies revealed the reduction in crystallinity of pure drug in solid dispersions associated with diluting effect of polymer. The results also revealed that the preparation conditions did not make significant polymorphic changes or amorphization of drug within the polymer network. The release of highly water soluble PHC can not be controlled at lower polymer ratio but was markedly sustained in coevaporates using RLPO at higher ratio following better fit to zero order release kinetics. Drug: RLPO coevaporates in 1:5 ratio could extend release of freely water soluble drug and could be successfully incorporated to formulate directly compressible tablets. The studies provide better forecasting and understanding of particulate systems to be incorporated to develop delivery systems.

**References**