Research Article

Investigation of \textit{In vitro} Release Kinetics of Carbamazepine from Eudragit\textsuperscript{®} RS PO and RL PO Matrix Tablets

Apurba Sarker Apu\textsuperscript{1*}, Atiqul Haque Pathan\textsuperscript{1}, Dilasha Shrestha\textsuperscript{2}, Golam Kibria\textsuperscript{2} and Reza-ul Jalil\textsuperscript{2}
\textsuperscript{1}Department of Pharmacy, East West University, Mohakhali, Dhaka-1212, \textsuperscript{2}Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

Abstract

\textbf{Purpose:} The objective of this research work was to prepare and evaluate the effect of Eudragit RS PO and Eudragit RL PO polymers on the physical property and release characteristics of carbamazepine matrix tablets.

\textbf{Methods:} Matrix tablets containing carbamazepine were prepared with Eudragit\textsuperscript{®} RS PO alone as the rate-retarding polymer (coded batch series ‘A’) and also with a combination of Eudragit\textsuperscript{®} RS PO and RL PO (coded batch series ‘B’). The tablets were characterized for hardness as well as for carbamazepine release. The release data were subjected to different models in order to evaluate their release kinetics and mechanisms.

\textbf{Results:} The hardness of batch series ‘A’ matrix tablet was >160 kg/cm\textsuperscript{2} while for batch series ‘B’, it was >170 kg/cm\textsuperscript{2}. Carbamazepine tablets containing only Eudragit RS PO showed very slow release (less than 6% in 8 h) but when Eudragit RL PO was blended with Eudragit RS PO, the release rate improved significantly to 44% in 24 h (p < 0.05). Drug release mechanism was a complex mixture of diffusion and erosion.

\textbf{Conclusion:} Carbamazepine matrix tablets of satisfactory hardness were produced. Furthermore, by blending Eudragit RS PO with Eudragit RL PO in the matrix, tablets of varying release characteristics can be prepared.

\textbf{Keywords:} Carbamazepine, Matrix tablet, Hardness, Eudragit\textsuperscript{®} RS PO, Eudragit\textsuperscript{®} RL PO, Release kinetics.
Introduction

Biopharmaceutics Classification System (BCS) class II drugs exhibit low solubility and high permeability characteristics. Their oral absorption is mostly governed by in vivo dissolution; the solubility and the dissolution rate are therefore key determinants for the oral bioavailability of these drugs. This implies that a small increase in the dissolution rate will result in a multi-fold increase in bioavailability.

Carbamazepine, a dibenzapine derivative with a structure resembling the tricyclic antidepressants, an effective anti-epileptic drug, belongs to the BCS class II, a feature of which is low aqueous solubility (~170 mg/L at 25°C). Due to poor water solubility, its absorption is dissolution rate-limited, which often results in irregular and delayed absorption. Carbamazepine has a narrow therapeutic window and a large diurnal variation in plasma concentration is observed. Conventional tablets need to be administered 3-4 times a day and a sustained release (SR) preparation decreases side effects (by elimination of the peaks and troughs in plasma drug concentration) and improves compliance (by decreasing the frequency of administration). Plastic polymers, e.g., ethylcellulose and acrylates, which are capable of forming insoluble or skeleton matrices, have been widely used for controlled release of drugs due to their inertness and drug embedding ability. Liquid penetration into the matrix is the rate-controlling step in such systems, unless channeling agents are used.

Acrylic polymers are widely used as tablet coatings and as retardants of drug release in sustained released formulations. The most interesting acrylic polymers are high permeable Eudragit RL and low permeable Eudragit RS, both of which are neutral co-polymers of poly (ethylacrylate, methyl methacrylate) and trimethyl aminoethyl methacrylate chloride, and are insoluble in water and digestive juices; but they swell and are permeable, which means that drugs embedded in their matrices can be released by diffusion. Therefore, the permeability of drug through Eudragit RS and/or RL is independent of the pH of the digestive tract. The degree of permeability depends on the relative proportion of quaternary ammonium groups in Eudragit. The proportion of functional quaternary ammonium groups in Eudragit RL and Eudragit RS is 10 and 5%, respectively. Eudragit RL PO and RS PO are fine, white powders with a slight amine-like odor. They are characteristically the same polymers as Eudragit RS and RL.

The aim of this work was to prepare uncoated plastic matrix tablets containing carbamazepine as a model drug, and Eudragit RS PO and Eudragit RL PO as plastic matrix to retard drug release. Another objective of this work was to evaluate drug release data using various kinetic models in order to determine the mechanism of drug release.

Materials and Methods

Carbamazepine (BDH, UK) was a gift from Eskayef (SK+F) Bangladesh Limited. Eudragit RL PO and Eudragit RS PO (BASF, Germany), Ludipress LCE - a lactose-based direct compression excipient used for modified release formulations (BASF, Germany), magnesium stearate (BDH, UK), talc (BDH, UK), Aerosil (BASF, Germany) and all other solvents and chemicals used, were of reagent grade.

Preparation of carbamazepine matrix tablets

The carbamazepine matrix formulations were composed as shown in Table 1. Batch series ‘A’ consisted of tablets made with Eudragit RS PO alone as the matrix while the matrix of batch series ‘B’ tablets comprised of both Eudragit RS PO and RL PO. The mixture (for 20 tablets), in each case, was well mixed in a locally fabricated laboratory drum blending machine at 40 rpm for 10 min and then an equivalent amount of dry powder (808...
Table 1: Composition of carbamazepine matrix tablets

<table>
<thead>
<tr>
<th>Ingredient (mg)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
<th>A5</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
<th>B5</th>
<th>B6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Ludipress LCE</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Eudragit RS PO</td>
<td>400</td>
<td>350</td>
<td>300</td>
<td>250</td>
<td>200</td>
<td>160</td>
<td>140</td>
<td>120</td>
<td>100</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Eudragit RL PO</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
<td>140</td>
</tr>
<tr>
<td>Talc</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mg-stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Aerosil</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>808</td>
<td>808</td>
<td>808</td>
<td>808</td>
<td>808</td>
<td>810</td>
<td>810</td>
<td>810</td>
<td>810</td>
<td>810</td>
<td>810</td>
</tr>
</tbody>
</table>

Table 2: Mean hardness of batch series “A” and “B” matrix tablets

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Mean hardness (kg/cm²) ± SD</th>
<th>Batch code</th>
<th>Mean hardness (kg/cm²) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>193.92 ± 0.40</td>
<td>B1</td>
<td>169.76 ± 0.36</td>
</tr>
<tr>
<td>A2</td>
<td>217.64 ± 0.34</td>
<td>B2</td>
<td>199.43 ± 0.37</td>
</tr>
<tr>
<td>A3</td>
<td>176.53 ± 0.32</td>
<td>B3</td>
<td>216.14 ± 0.74</td>
</tr>
<tr>
<td>A4</td>
<td>206.16 ± 0.16</td>
<td>B4</td>
<td>204.97 ± 0.27</td>
</tr>
<tr>
<td>A5</td>
<td>161.57 ± 0.40</td>
<td>B5</td>
<td>197.83 ± 0.20</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>B6</td>
<td>178.73 ± 0.47</td>
</tr>
</tbody>
</table>

SD = standard deviation (n=5); The difference in mean tablet hardness between batch series ‘A’ and batch series ‘B’ was significant (p < 0.05), except for batches A2 and B3.

Evaluation of tablets

Hardness measurement

For each formulation, the hardness of 5 tablets was determined using an electronic hardness tester (Erweka TBH 28, Germany). The mean crushing strength (hardness) was determined and the data are presented in the Table 2.
In vitro release studies

In vitro drug release studies of the matrix tablets were conducted using a six-station USP XXII type 1 apparatus (Electrolab TDT-06, India) at 37°C (± 0.5°C) and 50 rpm speed in 1 L of distilled water as a dissolution medium. Six millilitre (6 ml) samples were taken by filtration at regular time intervals over a period of 480 minutes in the case of ‘A’ series matrix tablets and over period of 720 min for ‘B’ series tablets. After each sampling, the volume of the dissolution medium was replenished with 6 ml of distilled water. The absorbance of the samples, after filtration, was measured with a single-beam spectrophotometer (Shimadzu UV-1200, Japan) at 288 nm and amount of drug computed.

Mechanism of drug release

To determine the mechanism of drug release from the formulations, the data were treated according to zero-order\(^{12}\) (cumulative amount of drug released vs time, Eq 1) and the Highuchi\(^{13}\) (cumulative percent of drug released vs square root of time, Eq 2) models.

\begin{align*}
M_t &= M_0 + k_0 t \quad \text{(1)} \\
M_t &= M_0 + k_H t^{1/2} \quad \text{(2)}
\end{align*}

where \(M_t\) is the cumulative amount of drug released at any time, \(t\) and \(M_0\) is the dose of the drug incorporated in the delivery system. \(k_0\) and \(k_H\) are rate constants for zero-order and Higuchi models, respectively.

The dissolution data were also fitted according to the well-known exponential equation of Peppas et al.\(^{15}\) (Eq 3) which is often used to describe drug release behavior from polymeric systems.

\[ \frac{M_t}{M_\alpha} = k t^n \quad \text{(3)} \]

where, \(\frac{M_t}{M_\alpha}\) is the fraction of drug released at time, \(t\), \(k\) is the kinetic constant, and \(n\) is the diffusional exponent for drug release. The diffusional exponent, \(n\), is dependent on the geometry of the device as well as the physical mechanism for release. The values of \(n\) for a cylindrical shaped device are < 0.43 or 0.43 for Fickian release and 0.85 for case II or zero-order release in this model. For systems exhibiting case II transport, the dominant mechanism for drug transport is due to polymer matrix relaxation. The value of \(n > 0.43\) but < 0.85 is considered as anomalous transport (non-Fickian) and refers to the coupling of Fickian diffusion and polymer matrix relaxation. The value of \(n > 0.85\) is considered as super case II transport\(^{16}\).

Results

Hardness of matrix tablets

The hardness of batch series “A” matrix tablets of ranged from 161.57 to 217.64 kg/cm\(^2\) (Table 2) with matrix tablets A2, having Ludipress LCE and Eudragit RS PO in the ratio 1:7 exhibiting the highest value. Similarly, the hardness batch series “B” matrix tablets were varied from 169.76 to 216.14 kg/cm\(^2\). In this case, the highest hardness was recorded for matrix tablets B3 containing Eudragit RL PO and Eudragit RS PO in the ratio of 2:3. The difference between the mean tablet hardness of batch series ‘A’ and batch series ‘B’ was significant (p < 0.05), except for batches A2 and B3.

Drug release from matrix tablets

The cumulative release data for carbamazepine from batch series “A” matrix tablets show that less than 10% drug was released in 8 h (see Figure 1). However, addition of Eudragit RL PO to Eudragit RS PO (i.e., batch series “B”) enhanced release rates to as high as > 40% (Figure 2). Increase in Eudragit RL PO content up to 50% of the total
polymer matrix produce release rates that increased slowly and linearly (Figure 2) but this changed to a sudden and sharp rise in release rate when the proportion of Eudragit RL PO exceeded 50%. The release rate attained a value of approximately 45% in 12 h when Eudragit RL PO constituted 70% of the matrix. The release data obtained were fitted into various release kinetic models and the outcome is listed in Table 3.

**Discussion**

In view of the importance of carbamazepine in the treatment of epilepsy and trigeminal neuralgia, the preparation of a suitable sustained release dosage form would not only increase the efficacy of treatment and patient compliance but should also produce desirable blood concentrations and decrease the incidence of adverse effects.

It is well established that the hardness of the tablet can markedly affect the release rate of drug\(^{17}\). Since Eudragit polymers have plastic deformation properties and a tendency to coat drug particles, high compression forces result in hard tablets with low porosities. But at high compression forces, a continuous matrix is formed and the change in tablet hardness causes relatively small changes in porosity and, therefore, release rate\(^{18}\). A similar result was obtained with Eudragit matrix tablet by other researchers\(^{19}\).

Carbamazepine release from the Eudragit RS PO matrix tablets (batch series A) was very poor. This is attributable to the fact that carbamazepine is very poorly soluble drug in the dissolution medium\(^6\). Another reason is the fact that Eudragit RS PO is water insoluble and also has very low permeability\(^{11}\). Since this formulation did not contain any channeling agents, formation of pores and cracks did not occur to facilitate drug release.

**Release kinetics and mechanism of carbamazepine tablets containing Eudragit RS PO**

An ideal matrix formulation should contain polymers and diluents at amounts as little as possible, as well as releasing its content in a sustained release profile over a reasonable length of time, preferably with zero-order kinetics\(^19\). Carbamazepine release kinetics was determined by multiple coefficients \((R^2)\) for individual formulation (Table 3). From the correlation coefficient values, it appears that carbamazepine release mechanism from formula ‘A’ was mainly zero-order since it had a higher \(R^2\) value for the whole release process. The zero-order rate describes systems where drug release rate is independent of drug concentration\(^{14}\).

The diffusional exponent (see Table 3) of batches A1 and A2 imply that the release of carbamazepine was case II or zero-order transport. For systems exhibiting case II transport, the dominant mechanism for drug transport is due to polymer matrix relaxation. The diffusional exponent of batches A3, A4 and A5 indicates non-Fickian type of release mechanism, meaning that drug release couples Fickian diffusion with polymer matrix relaxation - so-called anomalous diffusion - and may indicate that drug release is controlled by more than one process.

**Release kinetics and mechanism of carbamazepine tablets containing Eudragit RS PO and Eudragit RL PO**

As Figure 1 shows, the release of drug increased with increase in the proportion of Eudragit RL PO which also translates to a corresponding decrease in the proportion of Eudragit RS PO. This was due to the increase in solubility of the drug as a result of the presence of a more hydrophilic carrier surrounding the drug particles.
Table 3: Drug release parameters for batch series “A” and “B” matrix tablets

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Zero-order</th>
<th>Higuchi</th>
<th>Diffusional exponent (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$k_0$ (min$^{-1}$)</td>
<td>$r^2$</td>
</tr>
<tr>
<td>A1</td>
<td>0.906</td>
<td>0.005</td>
<td>0.979</td>
</tr>
<tr>
<td>A2</td>
<td>0.995</td>
<td>0.008</td>
<td>0.967</td>
</tr>
<tr>
<td>A3</td>
<td>0.985</td>
<td>0.009</td>
<td>0.947</td>
</tr>
<tr>
<td>A4</td>
<td>0.994</td>
<td>0.010</td>
<td>0.972</td>
</tr>
<tr>
<td>A5</td>
<td>0.995</td>
<td>0.011</td>
<td>0.969</td>
</tr>
<tr>
<td>B1</td>
<td>0.959</td>
<td>0.011</td>
<td>0.996</td>
</tr>
<tr>
<td>B2</td>
<td>0.959</td>
<td>0.011</td>
<td>0.997</td>
</tr>
<tr>
<td>B3</td>
<td>0.975</td>
<td>0.014</td>
<td>0.966</td>
</tr>
<tr>
<td>B4</td>
<td>0.974</td>
<td>0.015</td>
<td>0.947</td>
</tr>
<tr>
<td>B5</td>
<td>0.922</td>
<td>0.033</td>
<td>0.800</td>
</tr>
<tr>
<td>B6</td>
<td>0.889</td>
<td>0.057</td>
<td>0.743</td>
</tr>
</tbody>
</table>

$k_0 =$ zero-order rate constant; $k_H =$ Higuchi rate constant

Figure 1: Comparative release profile of carbamazepine from batches A1 (…•…), A2 (…■…), A3 (…▲…), A4 (…×…), A5 (…*…). X = Zero-order plot; Y = Higuchi plot. Ratio of Ludipress LCE : Eudragit RS PO was: A1 (0:1), A2 (1:7), A3 (1:3), A4 (3:5), A5 (1:1).
From the correlation coefficient values (shown in Table 3), it appears that the Higuchi model seems the best-fitting model, which indicates a diffusion-controlled release. The erosion of the matrix tablet might have occurred due to the lower water solubility of the drug\(^{20}\), thus gradually reducing the diffusion path length, which in turn attenuates the decrease of the release rate in the Higuchi model, making the pattern to resemble zero-order model.

Burst release of carbamazepine occurred in B6 formula. This can be attributed to the hydrophilic nature of Eudragit RL PO. When exposed to the dissolution medium, the solvent penetrates into the free spaces between macromolecular chains of Eudragit RL PO. After solvation of the polymer chains, the dimensions of the polymer molecule increase due to polymer relaxation by the stress of the penetrated solvent.

The diffusional exponent (see Table 3) of batches B1 and B5 imply that release of carbamazepine was case II or zero-order transport. For systems exhibiting case II transport, the dominant mechanism for drug transport is due to polymer matrix relaxation. The diffusional exponent of batches B2, B3 and B4 indicates non-Fickian type of release mechanism i.e., drug release is by coupling of Fickian diffusion and polymer matrix relaxation - so-called anomalous diffusion - and may indicate that drug release is controlled by more than one process. The diffusional exponent of batch B6 (0.9196) indicates super case II transport. In super case II transport, the release curve is linear for an exponential function of the release versus time. The higher drug release rate of Eudragit RS PO and Eudragit RL PO combination matrix tablets (batch series ‘B’), compared to drug release from Eudragit RS PO matrix tablets (batch series ‘A’), may be attributed to the higher hydrophilic groups in Eudragit RL PO molecules, creating pores and channels and thus facilitating solvent penetration and elevation of drug release.

The carbamazepine matrix tablets did not fulfill the USP requirement for carbamazepine SR (sustained release) tablets, as it requires between 65% and 90% of the drug to be dissolved within 12 hours\(^{21}\). Pharmaceutical excipients can be used to improve drug solubility through various mechanisms, ranging from changing the pH in the microscopic environment surrounding drug particles, through affecting the physical state of drug molecules packed with each other.

---

**Figure 2:** Comparative release profile of carbamazepine from batches B1 (...●...), B2 (...★...), B3 (...▲...), B4 (...○...), B5 (...×...), B6 (...●...). X = Zero-order plot, Y = Higuchi plot. Ratio of Eudragit RL PO : Eudragit RS PO is: B1 (1:4), B2 (3:7), B3 (2:3), B4 (1:1), B5 (3:2), B6 (7:3).
facilitating wetting by intestinal fluid, to increasing solubility through emulsifying effects.

Conclusion

Eudragit RS PO and Eudragit RL PO have potentials for aiding the formulation of sustained-release carbamazepine matrix tablets. In most cases, the release kinetics of carbamazepine from the matrix tablets appeared to follow zero-order release kinetics. Insensitivity of the release profile to moderate changes in hardness should be of great importance in industrial production.

Acknowledgement

The authors wish to thank Eskayef (SK+F) Bangladesh Limited, Dhaka, for providing carbamazepine, and also Essential Drug Company Ltd (Dhaka, Bangladesh) for technical support.

References