Kinetics and mechanism of diazepam release from solid dispersions

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Abstract: According to the biopharmaceutics classification system, diazepam belongs to the class II drugs. Inadequate dissolution rate of diazepam can be the limiting factor for its absorption rate. The aim of the present study was preparation of diazepam solid dispersions using various carriers like polyethylene glycol 2000, polyethylene glycol 4000 and polyvinylpyrrolidone K30, estimation of solubility and dissolution rate of prepared diazepam solid dispersions and comparison of these data to that of pure diazepam. The solid dispersions were prepared by solvent evaporation method. Phosphate buffer pH 6.8 was used as dissolution medium. Solid dispersions of diazepam with polymers resulted in increased solubility and dissolution rate of diazepam (highest with polyvinylpyrrolidone K30). The rate release kinetics of diazepam from the solid dispersions followed Hixson-Crowell cube root law. The correlation coefficient (r²) values of the Hixson-Crowell’s cube root model were slightly higher (0.9665 to 0.9977) when compared to the zero and first order release model. The high values of regression coefficients suggested that all formulations followed Korsmeyer-Peppas model of release kinetics. The low values of the release exponent (≤ 0.45) indicated that the mechanism of diazepam release from all the formulations could be described as a Fickian diffusion mechanism.

INTRODUCTION

Diazepam (Dz), as the most representative benzodiazepine, is widely used as anticonvulsant, anxiolytic, sedative agent, hypnotic, muscle relaxant and is also very useful in suppressing febrile and epileptic convulsions (Riss, Cloyd, Gates, et al., 2008; Mandrioli, Mercolini, Raggi, 2008). According to biopharmaceutics classification system (BCS) of drugs, it belongs to the class II. It is almost insoluble in water, which was confirmed by the fact that the dissolution of its highest dose at pH values in range 1 - 7.4 at 37 °C required volume greater than 250 mL of water or a suitable aqueous medium. The value of the intrinsic dissolution rate of diazepam is less than 0.1 mg min⁻¹ cm², so drug dissolution would be the rate-limiting step to absorption (Hadžiabdić, Elezović, Hadžović, et al., 2013; Dyas and Shah, 2007). The improvements in solubility and/or dissolution rate/bioavailability of diazepam may be achieved through the preparation of solid dispersions (SDs).

The increase in solubility/dissolution rate from solid dispersions can be attributed to one or a combination of the following factors: reduction of particle size of the drug, solubilizing effect on the drug by the water soluble carriers due to increased wettability, improved dispersibility of the drug particles by using various hydrophilic carriers and the possible formation of a metastable dispersion that has a greater solubility resulting in faster dissolution rate. Drug release from solid dispersions is described in several ways. Immediate release drug products allow drugs to dissolve with no intention of delaying or prolonging dissolution or absorption of the drug. Among the popular carriers used in the formation of solid dispersion are polyethylene
glycol (PEG) and polyvinylpyrrolidone (PVP) (Kumar and Vandana, 2012; Tiwari, Tiwari, Srivastava, et al., 2009; Sapkal, Babbulkar, Ratli, et al., 2013). In the literature, various solid dispersions of diazepam are reported for improving the dissolution of diazepam using various carriers like polymers (Cwiertnia, 2008; Rabasco, Ginesh, Fernandez, et al., 1991; Verheyen, Blaton, Kingrt, et al., 2002).

Diazepam was formulated as solid dispersions (solvent evaporation technique) using 1:5, 1:10 and 1:20 ratios of drug and carriers. The objective of this investigation was to examine the influence of water-soluble polymers, like polyethylene glycol 2000 (PEG 2000), polyethylene glycol 4000 (PEG 4000) and polyvinylpyrrolidone K30 (PVP K30) on solubility and dissolution rate behavior of diazepam from solid dispersions. Diazepam content, saturation solubility study and in vitro dissolution rate of diazepam solid dispersions were analyzed. The in vitro dissolution study was carried out by USP paddle method (USP-NF, 2013), using phosphate buffer with a pH of 6.8 as the dissolution medium. The increase in solubility and dissolution rate of diazepam were observed in all diazepam solid dispersions when compared to pure diazepam. In order to predict and correlate the kinetics and mechanism of diazepam release from diazepam solid dispersions using polymers, it is necessary to fit dissolution date into a suitable mathematical model. The zero order, first order, Hixson-Crowell and Korsmeyer-Peppas models were used to fit the in vitro diazepam release date from the solid dispersions. The correlation coefficient (r²) was considered the main parameter for assessing the models. The diffusion coefficient (n) is indicative of transport mechanism (Gautam and Mahaveer, 2011).

**EXPERIMENTAL**

**Materials**

Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one) (M₁ = 284.75 g mol⁻¹, F.I.S. - Fabbrica Italiana Sinteticì, Italy), polyethylene glycol 2000 (M₁ ~ 1800-2200 g mol⁻¹, Merck KGaA, Germany), polyethylene glycol 4000 (M₁ ~ 3500-4500 g mol⁻¹, Merck KGaA, Germany), polyvinylpyrrolidone K30 (M₁ ~ 40000 g mol⁻¹, BASF ChemTrade GmbH, Germany), Acidum hydrochloricum fumans, 37%, pro analysi, (Merck KGaA, Germany), Disodium hydrogen phosphate (Merck KGaA, Germany), Potassium dihydrogen phosphate (Merck KGaA, Germany), Methanol, p. a., (Merck KGaA, Germany), Ethanol, 96% v/v (Sigma-Aldrich GmbH, Germany).

**Preparation of diazepam solid dispersions using polymers**

Solid dispersions of diazepam were prepared by solvent evaporation technique using various polymers as carriers in 1:5 (SD1, SD4, SD7), 1:10 (SD2, SD5, SD8) and 1:20 (SD3, SD6, SD9) ratios. Diazepam and polymers were separately dissolved in a minimum amount of methanol (class 2) to get clear solution on ultrasonic bath (Sonorex Digitec DT 512 H, Bandelin, GmbH, Germany) at room temperature (at 22 °C ± 2 °C). The solvent of the mixture of diazepam and polymers was removed by evaporation on Rotavapor R-205 (Buchi, Switzerland) at 40 °C. Evaporation of methanol was carried out under reduced pressure of 337 mbar, at 120 rpm/min. The samples were subjected to drying for a period of 6 hours in vacuum oven VD 23 (Binder, USA) at 40 °C ± 0.5 °C. The dried mass was sieved through sieve No. 20 (WS TylerR. Ohio, USA) (Lima, Soares-Sobrinho, Corrêa, et al., 2008; Kalyanwat and Patel, 2010; van Drooge, Hinrichs, Visser, et al., 2006). All SDs were kept at room temperature in screw-capped glass vials until use.

**Determination of percent diazepam content in solid dispersions**

Determination of content of diazepam in solid dispersions with PEG 2000, PEG 4000 and PVP K30 was carried out by weighing (Analytical balance type XS 205DU/A, Mettler Toledo GmbH, Germany) the equivalent of 0.005 mg mL⁻¹ of diazepam in 0.1 mol L⁻¹ hydrochloric acid. Solid dispersions of diazepam were placed in 50 mL volumetric flasks. Ethanol (10 mL) was added and samples were mixed on the magnetic stirrer (Magnetic stirrer C - MAG HP 7, IKA® Werke GmbH, Germany) at room temperature for 20-30 minutes. The volume was filled to the mark with ethanol. After that, 1 mL of these solutions was suitably diluted with 0.1 mol L⁻¹ hydrochloric acid in 100 mL volumetric flask. The samples were spectrophotometrically assayed, using Varian Cary 50, UV-VIS spectrophotometer (Varian, Inc., USA), for diazepam content at 241 nm (Calibration curve for diazepam: concentration range: 2 - 10 × 10⁻⁷ mg mL⁻¹, r² = 0.9999). To nullify the absorbance due to the presence of polymers, the apparatus was calibrated with the corresponding blank in every assay. Each preparation was tested in triplicate and the mean values were calculated (Table 1).

**Determination of saturation solubility**

Solubility measurements and the determination of saturation concentrations were carried out by addition of excess amounts of diazepam solid dispersions (Analytical balance type XS 205DU/A, Mettler Toledo GmbH, Germany) to phosphate buffer solution (pH meter SevenMultiTM S47-K, Mettler Toledo GmbH, Germany). The phosphate buffer solution is simulated intestinal fluid without enzymes, the pH value 6.8. The samples were shaken at 200 rpm/min, during 24 hours on thermostated shaking bath (BDL, Type: GFL 1083, Czech Republic), to reach equilibrium, at 37 °C ± 0.1 °C (USP-NF, 2013; ,US FDA, CDER, 2000; Wagh and Patel, 2010). The samples were then filtered (Cellulose acetate filter, Sartorius, Germany), suitably diluted and analyzed on Varian Cary 50 UV-VIS spectrophotometer (Varian, Inc., USA) at 230 nm wavelength (Table 2).

**In vitro dissolution studies**

In vitro dissolution studies were performed in phosphate buffer (pH 6.8, 900 mL) at 37 ± 0.5 °C, using dissolution tester (Dissolution Tester, Varian VanKel VK 7025, Varian, Inc., USA) type II (paddle method) (USP-NF, 2013). The agitation speed was set at 50 rpm. The samples (pure diazepam and diazepam solid dispersions) equivalent to 36 mg of diazepam were subjected to dissolution. At fixed time intervals, samples (5 mL) were
withdrawn and equal amount of fresh dissolution medium was added, pre-warmed to 37 °C. After appropriate dilution, the samples were filtered (Filters, Quality Lab Accessorius L.L.C., Varian, Inc., SAD) and spectrophotometrically assayed for diazepam content at 230 nm wavelengths using Varian Cary 50, UV-VIS spectrophotometer (Varian, Inc., USA). Experiments for dissolution studies were performed for 60 min (Table 3).

Drug release kinetics
To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as the cumulative amount of drug released vs. time, first order, as log cumulative percent drug remaining vs. time, describing concentration dependent drug release from the system (Equation 2).

\[ Q_r = Q_o - k_o \cdot t \]  
(1)

where is
- \( Q_r \) - concentration of drug dissolved in time,
- \( Q_o \) - initial concentration of drug in solution,
- \( k_o \) - zero order release constant,
- \( t \) - time.

\[ \ln Q_r = \ln Q_o - k_1 \cdot t \]  
(2)

where is
- \( Q_r \) - cumulative percent of drug remaining,
- \( Q_o \) - initial concentration of drug,
- \( k_1 \) - first order rate constant,
- \( t \) - time (Gautam and Mahaveer, 2011; Sahoo, Chakrabarti, Behera, 2012; Singh, Gupta, Kaur, 2011).

To evaluate the drug release from systems with polymer erosion/dissolution with changes in the surface area and the diameter of the particles or tablets, the data were also plotted using the Hixson-Crowell cube root law:

\[ Q_r^{1/3} - Q_o^{1/3} = k_{HC} \cdot t \]  
(3)

where is
- \( Q_r \) - concentration of drug released in time \( t \),
- \( Q_o \) - initial concentration of drug in the pharmaceutical dosage form,
- \( k_{HC} \) - rate constant for the Hixson-Crowell rate equation.

The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets (Gautam and Mahaveer, 2011; Hixson and Crowell, 1931).

Mechanism of drug release
To study the drug release kinetics from polymeric systems the equation derived by Korsmeyer, Gurney, Doelker, et al., (1983) was used.

\[ \frac{Q_r}{Q_o} = k_{KP} \cdot t^n \]  
(4)

where is
- \( Q_r \) - fraction of drug released at time \( t \),
- \( Q_o \)
- \( k_{KP} \) - the rate constant for the Korsmeyer-Peppas,
- \( n \) - the release exponent indicative of the drug release mechanism,
- \( t \) - time.

If \( n \) value has the limiting values of 0.45 or less, the release mechanism follows Fickian diffusion and higher values of 0.45 to 0.89 for mass transfer follow a non-Fickian model or anomalous mechanism of drug release. The drug release follows zero-order drug release and case II transport if the \( n \) value is 0.89. For the values of \( n \) higher than 0.89, the mechanism of drug release is regarded as super case II transport (relaxation). The \( n \) value could be obtained from slope of the plot of log cumulative % of drug released vs. log time (Korsmeyer, Gurney, Doelker, et al., 1983; Suvakanta, Padala, Lilakanta, et al., 2010).

RESULTS AND DISCUSSION

Determination of percent diazepam content in solid dispersions
The content of diazepam in each preparation was assayed by UV spectroscopy. The drug content percentage in various newly prepared diazepam solid dispersions ranged from 93.33 ± 0.74% and 99.67 ± 0.45%, as reported in Table 1.

<table>
<thead>
<tr>
<th>Diazepam solid dispersions</th>
<th>Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dz : PEG 2000 1:5</td>
<td>93.33 ± 0.741</td>
</tr>
<tr>
<td>Dz : PEG 2000 1:10</td>
<td>99.38 ± 0.771</td>
</tr>
<tr>
<td>Dz : PEG 2000 1:20</td>
<td>96.00 ± 0.524</td>
</tr>
<tr>
<td>Dz : PEG 4000 1:5</td>
<td>98.00 ± 0.576</td>
</tr>
<tr>
<td>Dz : PEG 4000 1:10</td>
<td>96.00 ± 0.458</td>
</tr>
<tr>
<td>Dz : PEG 4000 1:20</td>
<td>96.33 ± 0.852</td>
</tr>
<tr>
<td>Dz : PVP K30 1:5</td>
<td>96.18 ± 0.482</td>
</tr>
<tr>
<td>Dz : PVP K30 1:10</td>
<td>97.33 ± 0.584</td>
</tr>
<tr>
<td>Dz : PVP K30 1:20</td>
<td>99.67 ± 0.450</td>
</tr>
</tbody>
</table>

All the solid dispersions showed the presence of high drug content and good uniformity of method employed for preparation. The method used in this study appears to be reproducible for preparation of diazepam solid dispersions.
Determination of saturation solubility
The solubility of diazepam solid dispersions in phosphate buffer at 37 °C are given in Table 2.

Table 2: Solubility of solid dispersions of diazepam with polymers (PEG 2000, PEG 4000 and PVP K30)

<table>
<thead>
<tr>
<th>Solid dispersions of diazepam with polymers</th>
<th>A</th>
<th>Concentration of diazepam (mg mL&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>SD&lt;sub&gt;SD&lt;/sub&gt;/SD&lt;sub&gt;Dz&lt;/sub&gt; b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dz : PEG 2000 1:5</td>
<td>0.559</td>
<td>0.0523 ± 0.072</td>
<td>1.13</td>
</tr>
<tr>
<td>Dz : PEG 2000 1:10</td>
<td>0.602</td>
<td>0.0572 ± 0.14</td>
<td>1.24</td>
</tr>
<tr>
<td>Dz : PEG 2000 1:20</td>
<td>0.632</td>
<td>0.0597 ± 0.22</td>
<td>1.29</td>
</tr>
<tr>
<td>Dz : PEG 4000 1:5</td>
<td>0.675</td>
<td>0.0578 ± 0.22</td>
<td>1.18</td>
</tr>
<tr>
<td>Dz : PEG 4000 1:10</td>
<td>0.655</td>
<td>0.0575 ± 0.20</td>
<td>1.19</td>
</tr>
<tr>
<td>Dz : PEG 4000 1:20</td>
<td>0.629</td>
<td>0.0593 ± 0.35</td>
<td>1.28</td>
</tr>
<tr>
<td>Dz : PVP K30 1:5</td>
<td>0.489</td>
<td>0.0907 ± 0.12</td>
<td>1.96</td>
</tr>
<tr>
<td>Dz : PVP K30 1:10</td>
<td>0.567</td>
<td>0.1067 ± 0.66</td>
<td>2.31</td>
</tr>
<tr>
<td>Dz : PVP K30 1:20</td>
<td>0.319</td>
<td>0.1202 ± 0.32</td>
<td>2.60</td>
</tr>
</tbody>
</table>

<sup>a</sup>Absorbance, <sup>b</sup>SD<sub>SD</sub>/SD<sub>Dz</sub> - Solubility enhancement factor calculated as the ratio of solid dispersion solubility (SD<sub>SD</sub>) in phosphate buffer solution versus diazepam solubility value (SD<sub>Dz</sub>) measured in the absence of polymer.

The solubility of diazepam is increased with increasing amount of polymers in solid dispersions (Table 2). The results of saturation solubility in phosphate buffer solution indicated that the solubility was increased by 2.60 fold with Dz : PVP K30 solid dispersion 1:20 ratio compared to solubility of pure diazepam (0.0462 ± 0.02 mg mL<sup>-1</sup>, 37 °C ± 0.1 °C) (Hadžiabdić et al., 2013).

Release rate studies
The in vitro dissolution characteristics of different types of diazepam formulations (with PEG 2000, 4000 and PVP K30) were compared with the pure drug. Dissolution profiles of diazepam and its solid dispersions are given in Table 3 as the mean concentrations of dissolved diazepam (%) for all solid dispersions (n = 3).

A plot of percent (%) diazepam released vs. time for the dissolution rate in accordance with zero order kinetics is shown in Figure 1, where the phosphate buffer solution pH 6.8 was used as a dissolution medium.

A linear plot of log percent (%) remaining vs. time from dissolution rate in accordance with first order equation is shown in Figure 2.

Table 3: Dissolution date of diazepam and diazepam solid dispersions

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Dz</th>
<th>SD1</th>
<th>SD2</th>
<th>SD3</th>
<th>SD4</th>
<th>SD5</th>
<th>SD6</th>
<th>SD7</th>
<th>SD8</th>
<th>SD9</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2.60</td>
<td>13.15</td>
<td>18.75</td>
<td>24.50</td>
<td>15.35</td>
<td>22.52</td>
<td>25.37</td>
<td>41.95</td>
<td>47.48</td>
<td>55.22</td>
</tr>
<tr>
<td>20</td>
<td>2.65</td>
<td>13.63</td>
<td>20.04</td>
<td>24.91</td>
<td>15.55</td>
<td>23.44</td>
<td>26.28</td>
<td>42.36</td>
<td>48.77</td>
<td>55.76</td>
</tr>
<tr>
<td>30</td>
<td>2.74</td>
<td>14.31</td>
<td>21.22</td>
<td>25.04</td>
<td>15.98</td>
<td>24.63</td>
<td>26.98</td>
<td>43.22</td>
<td>49.81</td>
<td>56.34</td>
</tr>
<tr>
<td>40</td>
<td>2.84</td>
<td>14.55</td>
<td>21.96</td>
<td>25.78</td>
<td>16.82</td>
<td>25.60</td>
<td>28.09</td>
<td>44.15</td>
<td>51.20</td>
<td>56.78</td>
</tr>
<tr>
<td>50</td>
<td>2.90</td>
<td>15.08</td>
<td>22.55</td>
<td>26.08</td>
<td>17.12</td>
<td>26.02</td>
<td>29.25</td>
<td>44.65</td>
<td>53.04</td>
<td>56.86</td>
</tr>
<tr>
<td>60</td>
<td>2.99</td>
<td>15.25</td>
<td>23.22</td>
<td>26.65</td>
<td>17.68</td>
<td>26.88</td>
<td>29.80</td>
<td>45.31</td>
<td>53.85</td>
<td>57.94</td>
</tr>
</tbody>
</table>

Figure 1: Zero order dissolution plots of diazepam and its solid dispersions

Figure 2: First order dissolution plots of diazepam and its solid dispersions
Dissolution of the diazepam in pH 6.8 phosphate buffer was only 2.99% after 60 minutes. After 60 minutes, solid dispersions of PEG 2000 and PEG 4000 (1:5, 1:10 and 1:20) showed 15.25%, 23.22%, 26.65%, 17.68%, 26.88% and 29.80% diazepam released, whereas solid dispersions with PVP K30 showed 45.31%, 53.85% and 60.26% diazepam released, whereas solid dispersions containing PVP K30 was increased as the ratio of PVP K30 increased (Figure 1). The correlation coefficient values of the Hixson-Crowell’s cube root model are found to be (r² = 0.967 to 0.998) slightly higher when compared to the zero and first order (Table 4) release model. Hence the release of drug from the preparations followed predominantly Hixson-Crowell cube root law compared to zero and first order kinetics. The high values of correlation coefficient (Table 4) suggested that all formulations followed Korsmeyer-Peppas model release kinetics. The values of correlation coefficient were found to be from 0.877 to 0.994. The n values for Korsmeyer-Peppas model were 0.0204 to 0.1196, indicating Fickian release (Table 4 and Figure 4). The low values of n (< 0.45) indicated that the mechanism of drug release from all the formulations could be described as a Fickian diffusion mechanism. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to the chemical potential gradient (Gautam, et al., 2011).

The correlation coefficient (r²) values in the analysis of dissolution data of diazepam solid dispersions as per zero order, first order, Hixson-Crowell cube root models and Korsmeyer-Peppas model are given in Table 4.

The correlation coefficient values of the Hixson-Crowell’s cube root model are found to be (r² = 0.967 to 0.998) slightly higher when compared to the zero and first order (Table 4) release model. Hence the release of drug from the preparations followed predominantly Hixson-Crowell cube root law compared to zero and first order kinetics. The high values of correlation coefficient (Table 4) suggested that all formulations followed Korsmeyer-Peppas model release kinetics. The values of correlation coefficient were found to be from 0.877 to 0.994. The n values for Korsmeyer-Peppas model were 0.0204 to 0.1196, indicating Fickian release (Table 4 and Figure 4). The low values of n (< 0.45) indicated that the mechanism of drug release from all the formulations could be described as a Fickian diffusion mechanism. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to the chemical potential gradient (Gautam, et al., 2011).
CONCLUSION

Solvent evaporation method of preparation resulted in diazepam solid dispersions with uniform content. The determination of saturation solubility and in vitro dissolution study showed that the solid dispersions increased solubility and dissolution rate of diazepam. Selected hydrophilic carrier polyvinylpyrrolidone K30 resulted in greater enhancement in solubility and dissolution rate of poorly soluble diazepam when compared with other polymer dispersions. Polymer dispersion dissolution studies can provide vital information on drug release mechanisms. The in vitro dissolution of diazepam from these solid dispersions was found to follow Hixson-Crowell model ($r^2 = 0.967$ to 0.998) signifying that the drug release from the solid dispersions was erosion based, due to the decrease in surface area and diameter of particles with polymer erosion. The high values of regression coefficients ($r^2 = 0.877$ to 0.994), suggested that all formulations followed Korsmeyer-Peppas model of release kinetics. The low values of the release exponent ($< 0.45$) indicated that the mechanism of diazepam release from all formulations could be described as a Fickian diffusion mechanism. The Fickian release was possible in all the formulation indicating polymer relaxation followed by diffusion of diazepam. It can concluded that water-soluble polyvinylpyrrolidone K30 can be used as polymeric carrier and to obtain faster dissolution of diazepam in form of solid dispersion for its pharmaceutical applications.

REFERENCES


Summary/Sažetak

Prema biofarmaceutskom sistemu klasifikacije diazepam spada u lijekove klase II. Neadekvatna brzina otapanja diazepamova može biti ograničavajući faktor za njegovu brzinu apsorpcije. Cilj ovog istraživanja je bio da se pripreme čvrste disperzije diazepamova koristeći razne nosače kao što su polietilenglikol 2000, polietilenglikol 4000 i polivinilpirolidon K30, procijeni topivost i brzinu otapanja pripremljenih čvrstih disperzija diazepamova i uporede podaci sa podacima čistog diazepamova. Čvrste disperzije su izrađene metodom evaporacije otapala. Kao disolucijski medij korišten je fosfatni pufer pH 6.8. Čvrste disperzije diazepamova s polimerima pokazuju povećanu topivost i brzinu otapanja diazepamova (najviše disperzija sa polivinilpirolidonom K30). Brzina kinetike oslobađanja diazepamova iz čvrstih disperzija slijedi Hixson-Crowell-ov zakon kubnog korijena. Vrijednosti koeficijenata korelacije ($r^2$) Hixson-Crowell-ovog modela kubnog korijena su nešto više (0.9667-0.9977) u odnosu na modele oslobađanja nultog i prvog reda. Visoke vrijednosti koeficijenata regresije sugerišu da sve formulacije slijede Korsmeyer-Peppas model kinetike oslobađanja. Niske vrijednosti eksponenta oslobađanja (< 0.45) ukazuju da se mehanizam oslobađanja diazepamova iz svih formulacija može opisati Fick-ovim mehanizmom difuzije.