Effect of casein incorporation on the release of diltiazem HCl from hypromellose-based matrix tablets

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ABSTRACT

This study aimed to investigate the modifying effect of casein (CAS) on the release of a model basic drug, diltiazem HCl (DTZ), from hydroxypropyl methylcellulose (HPMC) matrices. The interaction of DTZ and CAS in solution was investigated in terms of its stability and capacity using equilibrium dialysis. Granules made using different ratios of DTZ and CAS were prepared using wet granulation then compressed into matrix tablets.

The interaction between DTZ and CAS was found to have an association constant of 21.09 mM and a binding capacity of 0.4358 mg DTZ/mg CAS. The characterization of granules using differential scanning calorimetry (DSC), suggested interaction in solid state manifested by the loss of the melting endotherm of DTZ.

The effect of the pH and ionic strength of different dissolution media on drug release from tablets was also evaluated. With increasing content of CAS, the release of DTZ was observed to be less sensitive to the pH of the dissolution medium. Ionic interaction was confirmed by the accelerated release of DTZ from CAS-containing formulations in dissolution media with high ionic strength, indicative of an ion exchange process.

Keywords: Casein, Hypromellose matrix tablets, Diltiazem HCl, pH independence release.

1. INTRODUCTION

Numerous drugs used in clinical practice may be classified as weak bases or salts of weak bases. As such, they exhibit pH-dependent solubility in the pH range of the gastrointestinal (GI) tract. The increasing pH of GI fluids as the dosage form moves through the gastrointestinal tract may result in a decrease in the release rate of these drugs from conventional matrix tablets.¹²³⁴ Such pH-dependent release may have significant effects on the absorption of drugs, resulting in variability of drug release in vivo and bioavailability problems.⁵

On the other hand, a pH-independent release from controlled-release dosage forms is expected to build greater control of drug release from the dosage form. Different formulation approaches have been used to address this issue. Most of these approaches depend on the incorporation of an acidic excipient in matrix tablet formulations. Such acidic excipients may be either low molecular weight organic acids,¹²³⁴⁶ water-soluble polymers or water-insoluble polymers.²⁷⁸ Such excipients modify drug release in the pH range of GI fluids by either one of two processes. In one process, the excipient may be ionized at an intestinal pH, becoming more soluble and leaching from the gel layer of the matrix, making it less rigid and more hydrated, allowing for faster drug diffusion through the gel layer, thus compensating for the lower solubility of the drug. In the other process, the excipient may enhance drug solubility in the intestinal media by keeping the micro-environmental pH inside the gel layer and around dissolving drug particles more acidic than the bulk pH.

Other approaches to controlling drug release depend on the pH-dependent swelling and gelling of polymeric

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Received on 30/5/2017 and Accepted for Publication on 10/12/2017.
carriers to compensate for changes in the solubility of weakly basic drugs.\textsuperscript{9,10,11} As an example, the increased swelling and water uptake and reduced diffusional resistance of the matrix-forming polymer sodium alginate may help maintain a constant release rate of the weakly basic drug verapamil HCl as the pH of the dissolution medium increases, despite a reduction in the solubility of the drug.\textsuperscript{11}

Another, alternative approach that involves the interaction between the anionic functionalities of polymeric excipients and the cationic basic drugs has been used to achieve pH-independent release from matrix tablets. In such cases, drug release is significantly influenced by the dissociation of a complex formed between the drug and the ionized polymeric excipient, in addition to the standard effects of matrix gelling, matrix erosion, drug dissolution and drug diffusion. In these cases, drug release is more of an ion-exchange process rather than a pH-dependent dissolution process.\textsuperscript{8,12}

Because of their safety, abundance and diversity, natural proteins have been the subject of considerable attention for several years as a medium for controlled-release delivery of various drugs. One of the most important of the natural proteins is the milk protein casein (CAS).\textsuperscript{13,14,15,16} CAS is readily available, inexpensive, extremely stable and non-toxic.\textsuperscript{14} In addition, due to the fact that it is a phosphoprotein, CAS has the capability to interact with a wide range of active compounds with phosphate groups on its flexible linear polypeptide primary structure.\textsuperscript{13}

Diltiazem hydrochloride (DTZ) is a calcium channel blocking agent, effective in the management of hypertension and angina pectoris. DTZ has a moderately short biological half-life of 3 to-4 hours, and requires a rather high frequency of administration.\textsuperscript{17} One of the main challenges in formulating controlled-release DTZ products is diltiazem’s pH-dependent solubility (pK\textsubscript{a} = 8.91 ± 0.28) that is associated with bioavailability issues.\textsuperscript{17}

The purpose of the present study was to investigate the potential use of CAS as an excipient in releasing diltiazem hydrochloride from HPMC matrices, and to investigate the effect of the dissolution medium pH and ionic strength on DTZ release from these matrix tablets. The potential interaction of CAS and DTZ was also studied to investigate the hypothesized mechanism of pH-independent release.

**Experimental**

**Materials**

Diltiazem hydrochloride was generously donated generously by Dar Al Dawa (Naor, Jordan). Bovine milk casein was purchased from Sigma Life Science (St. Louis, USA). Vivapharm HPMC E 50 was donated by JRS Pharma (Germany). Lactose monohydrate was purchased from Fluka (Switzerland). Solvents and buffers salts were of analytical grade, were purchased from Gainland Chemical Company (UK) and were used in the condition they were received.

**Methods**

**Characterization of CAS-polymer interactions**

The interaction of CAS with DTZ was studied in water at 37°C by using a method described in the literature.\textsuperscript{8,12} Dialysis bags with a molecular weight cutoff of 14,000 Daltons (Membra-Cel MD 44-14, Viskase Companies Inc., Darien, IL) were filled with 10 mL of 50 mg% solution of CAS in USP purified water. The bags were closed and placed in 90 mL of DTZ solution under agitation at 37°C until equilibrium was established (24 hours).

The initial DTZ concentrations outside the dialysis bags ranged between 10 and 80 mg%. After equilibrium was reached, the drug concentration outside the dialysis bag was assayed by UV spectrophotometry at 237 nm using a SpectroScan 80D UV-VIS spectrophotometer (Biotech Co. Ltd., UK), and the amount of drug bound to the polymer was calculated by the difference between the initial and equilibrium concentrations.

The data were fit to the linearized form of the Langmuir adsorption equation (Equation 1)

$$\frac{1}{r} = \frac{1}{n} \frac{k_d}{n} \frac{1}{x}$$

(Equation 1),

Where $r$ is the amount of DTZ bound per mg of CAS at equilibrium, $x$ is the concentration of DTZ unbound (mg
%) at equilibrium, $k_d$ is the association constant, and $n$ is the maximum binding capacity for the drug (mg DTZ:mg CAS).

**Preparation of controlled-release matrix tablets**

CAS-containing, HPMC-based, DTZ matrix tablets, each containing 120 mg of DTZ, were prepared using a wet granulation procedure. The amount of CAS in the granulated mixtures were determined by the binding capacity of DTZ by CAS, with the amount of CAS in the different formulations capable of theoretically binding 100%, 50% or 0% of DTZ (Table 1).

<table>
<thead>
<tr>
<th>Amount (mg/tablet)</th>
<th>Formula A</th>
<th>Formula B</th>
<th>Formula C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem HCl</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Casein</td>
<td>275.36</td>
<td>137.68</td>
<td>0</td>
</tr>
<tr>
<td>HPMC</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Lactose</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

DTZ and CAS were passed through a No. 25 (opening size 710 μm) mesh sieve separately to remove any lumps. Afterwards, accurately weighed amounts of both components (together totaling 10 gm) were thoroughly mixed using mortar and pestle, followed by granulation using USP purified water as a granulating liquid. The formed granules were dried at 50°C overnight in a tray oven (Philip Harris Ltd, Shenstone, England), then sieved manually through a No. 25 mesh sieve.

The matrix tablets were prepared by passing the dried granules, HPMC, and lactose through a No. 25 mesh sieve to remove lumps, followed by manual mixing in a plastic bag for 5 minutes. Accurately weighed portions of the mixture, with a target weight of one tablet, were compressed in a 12-mm round die and flat punch set using a hydraulic press (Karl Kolb, Germany) with a compression force of 10 kN for 10 seconds.

Control formulations that did not contain CAS were manufactured using the same procedure as described above, except for the step of granulation of DTZ with CAS. Instead DTZ was dry mixed with HPMC and lactose.

**Differential scanning calorimetry**

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of samples of (i) DTZ; (ii) CAS; (iii) granules prepared from a mixture of CAS and DTZ, with an amount of CAS sufficient to complex with the total quantity of DTZ; (iv) granules using a mixture of CAS and DTZ, with an amount of CAS sufficient to complex with half of the amount of DTZ; and (v) a physical mixture of CAS and DTZ with an amount of CAS sufficient to complex with the total quantity of DTZ.

Samples (4 to 5 mg) were weighed and sealed into aluminum pans with pierced lids to allow the removal of water and other volatile substances. The samples were heated from 25 to 250°C with a heating rate of 10°C/min under nitrogen purge (80 mL/min) using a Mettler Toledo DSC 823 (Mettler, Switzerland).

**Drug release studies**

Dissolution studies were conducted in triplicate using a USP Type II dissolution apparatus (Erweka DT600, Germany) over a twelve-hour period. The stirring rate and temperature were adjusted to 100 rpm and 37±0.5°C, respectively. Drug release was evaluated in 900 mL of water, 0.9% NaCl, 0.1 N HCl, and USP phosphate buffer 6.8.

At predetermined time intervals, 5-mL samples were drawn for analysis. The removed volume was immediately replaced with an equivalent volume of fresh medium maintained at the same temperature. Samples were filtered.
through 0.45-µm nylon syringe filters, after which the absorbance of DTZ was measured at 237 nm (SpectroScan 80D, SpectroScan, USA). DTZ concentrations were calculated from linear calibration plots and used for the calculation of the percentage DTZ released at each time point. Mean values as well as standard deviations were calculated.

Dissolution profiles were compared using the similarity factor ($f_2$), presented in Equation 2. The $f_2$ statistic takes the average sum of squares of the difference between the test and reference profiles and fits the results between 0 and 100 when the test and reference are identical, and approaches zero as the dissimilarity increases.\textsuperscript{12,13}

\[
f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}
\]

………………..Eq. (2).

Where $n$ is the number of time points, $R_t$ is the dissolution value in 0.1 N HCl at time $t$, and $T_t$ is the dissolution value in USP phosphate buffer 6.8 at time $t$.

In addition, the kinetics of DTZ release from the various formulas was analyzed using the Korsmeyer-Peppas model\textsuperscript{18} given in Eq. (3),

\[
\frac{M_t}{M_{\infty}} = k t^n
\]

………………..Eq. (3),

Where $M_t/M_{\infty}$ is the fraction of drug released at time $t$, $k$ is the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery system and $n$ is the diffusional exponent which characterizes the transport mechanism of the drug.

In order to compare the release profile of different formulas with a possible difference in release mechanisms ($n$ values), a mean dissolution time (MDT)\textsuperscript{18} was calculated using Eq. (4), and the % difference between the MDT values for a single formula in 0.1 N HCl and phosphate buffer was calculated using Eq. (5).

\[
MDT = \frac{n}{(n + 1)(k^{1/n})} \quad \text{..........................Eq. (4).}
\]

The % difference was calculated as

\[
\% \Delta MDT = \left( \frac{MDT_{\text{buffer}} - MDT_{\text{acid}}}{MDT_{\text{buffer}}} \right) \times 100\% \quad \text{......Eq. (5).}
\]

The same data analysis was performed in comparing the release profiles of the matrices in deionized water (DIW) or normal saline 0.9 N NaCl (NS), where

\[
\% \Delta MDT = \left( \frac{MDT_{\text{NS}} - MDT_{\text{DIW}}}{MDT_{\text{DIW}}} \right) \times 100\% \quad \text{......Eq. (6).}
\]

Results and discussion

Characterization of CAS-DTZ interaction

The linearized form of the CAS-DTZ interaction isotherm in deionized water at 37°C is shown in Figure 1. The interaction was found to have an association constant of 21.09 mM and a binding capacity of 0.4358 mg of DTZ per 1 mg of CAS.

The affinity of DTZ for binding to CAS as described by the association constant is much higher than its affinity to bind to carrageenan (0.74 mM),\textsuperscript{12} and that of buspirone HCl to bind to chitosan succinate (2.001 mM).\textsuperscript{8} This suggests that CAS may be used effectively to modulate drug release from HPMC matrix tablets. However, the binding constant is comparable to that of tetrahydrozoline with polyacrylic acid (33.81 mM), and much less than that of tetrahydrozoline with hyalouronic acid (93.25 mM).\textsuperscript{19}

On the other hand, the binding capacity of the CAS-DTZ complex (0.4358 mg DTZ/mg CAS, equivalent to 1.05 µmol DTZ/mg CAS) was much higher than the binding capacity of buspirone HCl to chitosan succinate (0.002 µmol/mg), comparable to that of DTZ with carrageenan (3.71 µmol/mg), and much lower than that of tetrahydrozoline to either hyaluronic acid or polyacrylic acid (16.9 and 11.2 µmol/mg, respectively).\textsuperscript{8,12,19} The
limited binding capacity may be due to the limited surface area available for DTZ binding with CAS, as CAS is well-known to organize into spherical micelles with binding only possible on the exposed surface of the micelle.\textsuperscript{20}

Differential Scanning Calorimetry

Figure 2 shows the DSC thermograms of samples of (i) DTZ; (ii) CAS; (iii) granules prepared using mixtures of CAS and DTZ using an amount of CAS sufficient to complex with the total quantity of DTZ; (iv) granules prepared using mixtures of CAS and DTZ using an amount of CAS sufficient to complex with the half the quantity of DTZ; and (v) a physical mixture of CAS and DTZ with an amount of CAS sufficient to complex with the total quantity of DTZ.

The DTZ sample showed a sharp melting endotherm of DTZ at 217°C, while no clear thermal events were observed in the thermogram of CAS (Figure 2). The granulated CAS-DTZ with high CAS content showed a shallow peak at about 205°C, corresponding to the melting of the DTZ that had not interacted with CAS. In the physical mixture sample with the same composition, the intensity of the peak was increased and showed a smaller shift from the pure DTZ peak (peak at 212.7°C). This indicates that wet granulating DTZ and CAS results in a higher chance of interaction in comparison to simple physical mixing using mortar and pestle.

Increasing the amount of DTZ in the granules beyond the level corresponding to complete saturation of CAS resulted in granules with more free DTZ, and thermal behavior with a high-intensity DTZ peak, with a smaller shift (peak at 209°C) than the pure DTZ peak.

Dissolution of DTZ Tablets \textit{in vitro}

Figure 3 shows the release profiles of the three prepared formulations in 0.1 N HCl and USP phosphate buffer (pH 6.8). It may be deduced from Figure 1 that the drug release profiles of the same formula in the two media become closer to each other as the content of CAS increases.

This conclusion is supported by the use of the $f_2$ statistic. When comparing drug release in the acid and buffer media for each formula, the calculated $f_2$ value increased steadily as the CAS content in the formula...
increased. In formula C, which did not include CAS, the $f_2$ value between the buffer and acid profiles was 43.8, indicating a lack of similarity. When the same comparison was applied to formula B, which contained CAS-DTZ in a ratio theoretically sufficient to bind half of the DTZ to CAS, the $f_2$ value increased to 57.5, indicating similarity between the two profiles. The $f_2$ value reached 78.5 for formula A, which was made of granules of CAS-DTZ in a ratio theoretically sufficient to bind all of the DTZ to CAS, indicating increased similarity.
Figure 4. DTZ release from matrix tablets in deionized water (DIW) and normal saline 0.9% NaCl (NS). Each data point is an average of 6 samples. Error bars represent standard deviation

Table 2. Calculated dissolution parameters of DTZ from matrix tablets in acidic and buffer media

<table>
<thead>
<tr>
<th></th>
<th>Korsmeyer- Peppas model</th>
<th>Mean Dissolution Time, MDT (Hours)</th>
<th>% Δ MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>k (Hour^n)</td>
<td>n</td>
<td>R^2</td>
</tr>
<tr>
<td>A – PB pH 6.8</td>
<td>0.304</td>
<td>0.467</td>
<td>0.989</td>
</tr>
<tr>
<td>A – 0.1 N HCl</td>
<td>0.319</td>
<td>0.456</td>
<td>0.985</td>
</tr>
<tr>
<td>B – PB pH 6.8</td>
<td>0.366</td>
<td>0.440</td>
<td>0.989</td>
</tr>
<tr>
<td>B – 0.1 N HCl</td>
<td>0.391</td>
<td>0.518</td>
<td>0.996</td>
</tr>
<tr>
<td>C – PB pH 6.8</td>
<td>0.422</td>
<td>0.514</td>
<td>0.998</td>
</tr>
<tr>
<td>C – 0.1 N HCl</td>
<td>0.519</td>
<td>0.610</td>
<td>0.999</td>
</tr>
</tbody>
</table>
Table 3. Calculated dissolution parameters of DTZ from matrix tablets in deionized water (DIW) and normal saline 0.9 N NaCl (NS)

<table>
<thead>
<tr>
<th>Korsmeyer-Peppas model</th>
<th>K (Hour(^{-n}))</th>
<th>n</th>
<th>R(^2)</th>
<th>Mean Dissolution Time, MDT (Hours)</th>
<th>% Δ MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – DIW</td>
<td>0.214</td>
<td>0.604</td>
<td>0.998</td>
<td>4.845</td>
<td>-53.215</td>
</tr>
<tr>
<td>A – NS</td>
<td>0.354</td>
<td>0.565</td>
<td>0.993</td>
<td>2.267</td>
<td></td>
</tr>
<tr>
<td>B – DIW</td>
<td>0.315</td>
<td>0.524</td>
<td>0.996</td>
<td>3.116</td>
<td>-29.616</td>
</tr>
<tr>
<td>B – NS</td>
<td>0.401</td>
<td>0.478</td>
<td>0.988</td>
<td>2.193</td>
<td></td>
</tr>
<tr>
<td>C – DIW</td>
<td>0.388</td>
<td>0.536</td>
<td>0.998</td>
<td>2.042</td>
<td>-11.581</td>
</tr>
<tr>
<td>C – NS</td>
<td>0.413</td>
<td>0.539</td>
<td>0.989</td>
<td>1.806</td>
<td></td>
</tr>
</tbody>
</table>

In addition, fitting the dissolution profiles to the Korsmeyer-Peppas model (Table 2) showed an increase in the apparent release rate constant when the dissolution medium was 0.1 N HCl compared to the dissolution medium of USP phosphate buffer (pH 6.8). This may be explained based on the higher solubility of DTZ in the acidic medium.

One important limitation of using the apparent release rate constant of the Korsmeyer-Peppas model to make comparisons between different release profiles is the fact that the equation has two variables, the release rate constant (k) and the release exponent (n), with both values changing to achieve the best fitting curve. The comparison between different release profiles cannot be complete without including the two parameters. However, these variables may be combined by using the mean dissolution time (MDT), which includes both parameters.

The MDT values of the different formulations in both dissolution media are shown in Table 2. The MDT values were higher for dissolution profiles obtained from in buffer in comparison to those determined in the acidic medium. Another important parameter was the % difference in MDT between the dissolution profiles of formulations in buffer and acidic media, which decreased with increasing CAS content of the tablet formulation.

The presence of ions in the dissolution medium has previously been observed to increase dissolution rate from matrix systems, hindering the formation of the gel layer by competing for water molecules and salting out the polymer. This allowed faster penetration of water into the matrix and compromised the functional development of the gel layer as a diffusional barrier against the movement of the dissolved drug into the bulk solution. In addition, the presence of electrolytes in the dissolution medium may contribute to an ion exchange process where drug molecules are exchanged for salt ions, thus accelerating drug release via an ion-exchange mechanism.

In this study, the contribution of the ion-exchange mechanism on drug release was evaluated by performing the drug release studies in either deionized water (DIW) or normal saline 0.9% NaCl (NS). Drug release profiles of DTZ in DIW and NS are shown in Figure 4. DTZ release was observed to be faster using NS as a dissolution medium in comparison to DIW. This was confirmed by the dissolution data model fitting results (Table 3) where the apparent release rate constant was always higher in NS in comparison to DIW.

The effect of the presence of ions on drug release was more apparent in formulations containing DTZ granulated with CAS, which showed a major increase in drug release (Figure 4). The acceleration of DTZ release in NS was also observed to be dependent on CAS content of the formulation, with a more pronounced change in formula A, containing an amount of CAS sufficient for complete binding of DTZ, in comparison to formula B, containing an amount of CAS sufficient for binding half of the DTZ dose.

This is confirmed by the dissolution data model fitting results where the apparent release rate constant was always higher in NS in comparison to DIW. The %Δ MDT data
(Table 3) supported this conclusion as well, with the highest negative change in MDT observed in formula A, which contained CAS at the highest level. This suggested the significant involvement of ionic exchange with HPMC matrices containing CAS.

Conclusion

The anionic CAS was proved effective in modulating the release of DTZ from HPMC-based matrices. This was likely due to its ability to form a complex with the cationic drug. The stability of the CAS-DTZ complex and the complexation capacity was comparable to that between different anionic polymers and cationic drugs, and was proven sufficient to modulate drug release from HPMC matrices.

The inclusion of CAS in HPMC matrices decreased the difference in DTZ release rates when using 0.1 N HCl and USP phosphate buffer (pH 6.8) as release media. The efficacy of CAS in modulating DTZ release was dependent on the level of incorporation of CAS, with efficacy increasing as the level of CAS incorporation increased. Finally, the hypothesized nature of the ionic interaction and drug release mechanism were supported by observing an accelerated dissolution in media with higher ionic strengths. CAS is a novel material with positive potential for formulating cationic drugs in HPMC matrices with pH-independent target release.

Acknowledgement

The authors would like to acknowledge the generous support of the Deanship of Academic Research at the University of Jordan.

REFERENCES

Effect of casein incorporation...


تأثير الكازبين على إطلاق ديلتيازم هيدروكلوريد من حبوب الهيبروميثيلوز المضغوطة

إبتسام الحوامدة، أ.ب، البرقاوي، حاتم سمير الخطيب

كلية الصيدلة، الجامعة الأردنية، عمّان، الأردن.

ملخص

تهدف هذه الدراسة إلى التعرف على تأثير بروتين الكازبين على تحرير الدواء القاعدي ديلتيازم هيدروكلوريد من مضغوطات الدهون الرينية بروبيل ميثيل سيليلوز. تم دراسة ارتباط بين الديلتيازم والكازيين في الوسط المائي من ناحية سعة الارتباط وثباته. تم تحضير حطامات مكونة من الديلتيازم والكازيين باستخدام التحبيب الريفي وتم دراسة التفاعل بين الديلتيازم والكازيين في الحلقات باستخدام جهاز قياس الطاقة التفاعلية المسمى. تم خط حطامات الديلتيازم والكازيين مع هيدروكسي بروبيل ميثيل سيليلوز والاكسيتروز وضغطها على شكل أقراص دونية وتم تحليل دراسة إطلاق الديلتيازم من الأقراص دونية في أوساط مائية مختلفة لقياس اثر الرم الرئوي والتأثير الأولي لأوساط الأطقال على سرعة الأطقال. وجد أن الفاعل بين الديلتيازم والكازيين لديه معامل غليان يساوي 21.09 ملي مولار وسعة ارتباط تساوي 0.4358 ملم من الديلتيازم لكل ملم من الكازيين. استُخدمت الدراسة بواسطة جهاز قياس الطاقة التفاعلية المسمى عن الفاعل بين الديلتيازم والكازيين بتحفيز الإشارة الحرارية لإتصال الديلتيازم. لوحظ أن سعة أطقال الديلتيازم أصبحت أقل تأثيرًا بالرم الرئوي في وسط الأطقال المائي مع زيادة نسبة الكازيين. تم التأكد من طباعة الفاعل الأولي بين الديلتيازم والكازيين بتحفيز الإشارة السريع للديلتيازم من المستحضرات التي تحتوي على الكازيين في أوساط الأطقال المائية ذات التركيز الأولي العالي.

الكلمات الدالة: الكازيين، أقراص الهيبروميثيلوز المضغوطة، ديلتيازم هيدروكلوريد، إطلاق الدواء المستقل غير المعتمد على درجة الحوضة.

تاريخ استلام البحث: 30/5/2017 وتاريخ قبوله للنشر: 10/12/2017.