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Utilization of ionotropic gelation technique for bioavailability enhancement of cinnarizine: in-vitro optimization and in-vivo performance in human

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Abstract
Gastro retentive drug delivery system techniques were adopted to deliver drugs having narrow absorption window from a particular site in the GIT. Therefore, gastro retentive dosage forms were retained in the stomach, thus improving absorption and bioavailability would be improved consequentially. In this study, cinnarizine (CNZ) was employed as the model drug. CNZ is a poorly soluble basic drug, suffering from low and erratic bioavailability. This is attributed to its pH-dependant solubility (highly soluble at pH < 4). CNZ is characterized by short half-life (3–6h). Accordingly, floating CNZ emulsion gel calcium pectinate beads were developed. A mixture design was employed to study the effect of the percent of LM pectin (A), the percent of GMO (B) and the percent of Labrafac Lipophile (C) simultaneously on the percent of drug released and loaded. The optimized floating CNZ emulsion gel calcium pectinate beads and Stugeron® (the marketed reference product) were compared through a pharmacokinetic study carried out on healthy human volunteers. Fortunately, simple floating CNZ emulsion gel calcium pectinate beads were prepared with zero-order release profile for 12 h. A promising in-vivo CNZ controlled release dosage form with higher bioavailability, when compared to once daily administration of Stugeron® tablets was achieved.

Keywords
Gastro retentive dosage form, GMO, Labrafac Lipophil, LM pectin, mixture design

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Introduction
Oral controlled release (CR) dosage forms generally have a transit time of 1–3 h in the stomach, 3–5 h in the intestine and 4–11 h in the colon. However, some drugs require more retention time in the stomach for better results (Masaoka et al., 2006).

Gastro retentive dosage form can remain for several hours in the gastric region, thus prolonging the gastric residence time of some drugs. Improved bioavailability, reduction of drug waste and improved drugs solubility that are less soluble in a high-pH environment is a predicted result for prolonged gastric retention (Arora et al., 2005).

Cinnarizine (CNZ; class II of BCS) possess antihistaminic activity and mainly used for the control of vomiting due to motion sickness (Fernandez et al., 2009). CNZ-administering patients suffer from poor compliance due to its dosage regimen of 25 mg three times daily (Shidhaye, 2009).

CNZ is a weak basic drug possessing higher solubility at lower pH (0.29 mg/ml in 0.1 N HCl) and lower solubility at higher pH (0.002 mg/ml in phosphate buffer pH 7.2). Its main site of absorption is the stomach (upper part of GIT). In attempt to solve the above-mentioned problems of CNZ (model drug), floating drug delivery system for continuous delivery of CNZ in the stomach was suggested (Streubel et al., 2006).

Polysaccharides are widely used in oral drug delivery systems because of the simplicity to obtain the desired drug delivery system and drug release profile as a result of the insolubility of cross-linked beads in gastric environment (Roy & Shahiwala, 2009). Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form beads. In a work by Sriamornsak et al. (2008), a new emulsion gelation method was used to prepare oil-entrapped calcium pectinate gel (CaPG) beads as a carrier for intragastric floating drug delivery.

The aim of this research was to statistically optimize simple CNZ emulsion gel calcium pectinate beads using ionotropic gelation method. A mixture design was employed to optimize and study the effect of the percent of LM pectin (A), the percent of GMO (B) and the percent of Labrafac Lipophile (C) simultaneously on the percent of drug released and loaded. A pharmacokinetic study was carried out on healthy human volunteers to compare the optimized CNZ emulsion gel calcium pectinate beads and Stugeron® as the marketed reference product.
**Materials and methods**

**Materials**

CNZ HCl was supplied as a gift sample by Minapharm Pharmaceuticals Ltd. (Cairo, Egypt); LM pectins with DE of 36% (GENU pectin type LM101 AS) and 28% (GENU pectin type LM104 AS-FS) were obtained as gift sample from CP Kelco (Lille Skensved, Denmark) and are referred to as GP36 and GP28, respectively; Pecceol [Glyceryl monoleate (GMO)], liquid, HLB = 3], Labrafac Lipophile WL 1349 [(LL), liquid, medium chain triglycerides, HLB = 1] were obtained as gift sample from Gattefosse (St Priest, Cedex, France); hydrated calcium chloride, ethanol and sodium citrate were obtained from El-Nasser Company for Chemicals and Pharmaceuticals (Cairo, Egypt); hydrochloric acid (HCl) of analytical reagent grade and Stugeron® 25 mg tablets were purchased from the Egyptian market.

**Preparation of CNZ-loaded emulsion gel calcium pectinate beads using ionotropic gelation method**

CNZ-emulsion gel calcium pectinate beads were prepared by ionotropic gelation according to Sriamornsak’s method (Sriamornsak et al., 2008). Briefly, LM-pectin 101, LM-pectin 104, GMO, LL and distilled water were well stirred on a magnetic stirrer (model SP 72220-26, Barnstead/ Thermolyne, Dubuque, IA) at 500 rpm, an o/w emulsion was formed and then CNZ was dispersed. The formed o/w emulsion is then dripped via 23 gauge syringe in 100 ml 0.034 M CaCl₂ solution at a rate of 2 ml/min. The formed emulsion gel calcium pectinate beads were then filtered, collected and washed with distilled water for three times. Finally, the emulsion gel calcium pectinate beads were dried at 40°C for 12 h in glass vials.

**Experimental design**

A mixture experiment is a special type of response surface experiment in which the factors are the components of a mixture, and the response is a function of the proportions of each ingredient (Mura et al., 2005). The peculiar characteristic of a mixture design is that the single components cannot be changed independently of one another since their sum must add up to 100%. This means that mixture factors are expressed as the fraction of the total and their experimental ranges lie between 0 and 100% (Lewis et al., 1999; Mura et al., 2005).

Experimental design offers the benefit of obtaining highest amount of information with the lowest number of trials, which refers to the simultaneous study of the effect of different variables on the responses and interaction between them (Furlanetto et al., 2006). In the present study, the mixture experimental study was designed based on a three component system: the pectin base (A) (a mixture of LM-101/LM-104, 1:1 w/w), and the oil phase which is composed of: (B) (GMO) and (C) (Labrafac Lipophile WL-1349). The drug content was kept constant at 100 mg/10 g of the prepared calcium pectinate beads. The restrictions imposed on the mixture component proportions are shown in Table 1. Four responses were studied: the percent of drug released after 1, 5 and 8 h (Y₁, Y₂ and Y₃, respectively) and the percent of drug loaded (Y₄). Seven formulae were suggested by Minitab® software (version 16.1.1), duplicate experimentation was carried out. The results were expressed as mean ± standard deviation (SD).

**Drug loading**

Five hundred milligrams CNZ-pectin beads were initially sonicated with 3 ml (1% w/v) sodium citrate solution until complete dissolution, then 7 ml ethanol was added to the above solution to gel the solubilized calcium pectinate and further solubilize CNZ. This solution was filtered through millipore filter 0.2 µm. The filtrate was assayed for drug content by a validated UV spectrophotometer method at 253 nm using UV–visible spectrophotometer (Shimadzu, Japan) using ethanol as a blank after suitable dilutions (El-Kamel et al., 2003).

% Yield

The actual weight of beads was determined and compared to the theoretical one. The total yield was then calculated according to the following equation:

\[
\% \text{Yield} = \frac{\text{Actual wt.}}{\text{Theoretical wt.}} \times 100
\]

**In-vitro drug release study**

The release of CNZ from floating beads was determined in a USP paddle type (II) dissolution apparatus (Hanson Research, Chatsworth, CA). A weighed amount of beads equivalent to 25 mg drug was placed in the dissolution apparatus.

| Table 1. Independent and dependent variables of the D-optimal mixture design. |
|-----------------------------|-----------------------------|
| **Formulation variables**   | **Levels**                  |
| A: amount of LM pectin (g %)| Low                        | High                      |
|                            | 3                          | 7                         |
| B: amount of GMO (g %)      | 55                         | 85                        |
| C: amount of Labbrafac (g %)| 12                         | 38                        |
| **Response variables**      |                            | Constraints               |
| Y₁: Release (%) after 1 h  | 6.66% ≤ Y₁ ≤ 9.99%, target = 8.33% |
| Y₂: Release (%) after 5 h  | 37.49% ≤ Y₂ ≤ 45.83%, target = 41.66% |
| Y₃: Release (%) after 8 h  | 53.34% ≤ Y₃ ≤ 73.33%, target = 66.66% |
| Y₄: Loading efficiency (%) | 80% ≤ Y₄ ≤ 100%, Maximize  |

The amount of CNZ is kept constant at 100 mg/10 g.
Nine hundred milliliters of the 0.1 N HCl (pH 1.2) was used as the dissolution medium. The dissolution fluid was maintained at 37 ± 0.5°C at a rotation speed of 100 rpm. Five milliliters samples were withdrawn at specified intervals, passed through a 0.2-µm membrane filter (Millipore, Billerica, MA), and the initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. Samples were analyzed using a UV–visible spectrophotometer (Shimadzu, Japan) at 253 nm.

**Determination of swelling properties**

The swelling property of the beads was determined by placing the beads in the dissolution media (0.1 N HCl) for 8 h, and the swollen beads were collected, blotted with filter paper to remove absorbed water and then weighed immediately on an electronic balance. The percentage of swelling was then determined as in Equation (2) (Badve et al., 2007):

\[
\text{Swelling Index (SI)} = \frac{(W_t - W_0)}{W_0} \times 100
\]

### Analysis of the D-optimal mixture design

The responses of all model formulations were treated by Minitab® software (version 16.1.1). Suitable models for mixture designs consist of three components which include linear, quadratic and special cubic models.

For linear model:

\[
Y = b_1A + b_2B + b_3C \quad (3)
\]

For quadratic model:

\[
Y = b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC \quad (4)
\]

For special cubic model:

\[
Y = b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{123}ABC \quad (5)
\]

where \( Y \) is the dependent responses, \( b_1-b_{123} \) are the coefficients of the respective values to their interaction terms.

The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the standard deviation (SD), the multiple correlation coefficients (\( R^2 \)), adjusted multiple correlation coefficients (adjusted \( R^2 \)) and the predicted residual sum of square (PRESS) provided by Minitab® Software. Among them, PRESS indicates how well the model fits the data, and for the chosen model it should be small relative to the other models under consideration (Huang et al., 2004; Basalious et al., 2010).

### Scanning electron microscope

Optimized floating CNZ emulsion gel calcium pectinate beads were investigated using scanning electron microscope to visualize its surface morphology at different magnification powers. The sample for scanning electron microscope (SEM) was prepared by sticking the beads on a double adhesive tape, which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300 Å using a sputter coater (Jain & Gupta, 2009). These samples were then randomly scanned, and photomicrographs were taken.

### Floating time (floating behavior)

The gel beads (n = 20 beads) were placed in conical flasks with 50 ml 0.1 N HCl (pH 1.2). The flask was shaken at 100 rpm at 37°C in a shaking incubator. Their buoyancy was observed for 8 h.

---

**Table 2. The formulations of the mixture design and their characterization results.**

<table>
<thead>
<tr>
<th>Formula code</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>( Y_1 )</th>
<th>( Y_2 )</th>
<th>( Y_3 )</th>
<th>( Y_4 )</th>
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<tbody>
<tr>
<td>1</td>
<td>3.00000</td>
<td>85.0000</td>
<td>12.0000</td>
<td>18.63 ± 0.78</td>
<td>50.63 ± 1.29</td>
<td>63.33 ± 1.78</td>
<td>93.15 ± 0.85</td>
</tr>
<tr>
<td>2</td>
<td>3.00000</td>
<td>59.0000</td>
<td>38.0000</td>
<td>16.56 ± 1.14</td>
<td>45.42 ± 1.37</td>
<td>60.53 ± 2.56</td>
<td>84.15 ± 2.53</td>
</tr>
<tr>
<td>3</td>
<td>7.00000</td>
<td>71.1031</td>
<td>21.8969</td>
<td>21.89 ± 1.08</td>
<td>48.03 ± 1.80</td>
<td>62.99 ± 0.62</td>
<td>95.70 ± 0.46</td>
</tr>
<tr>
<td>4</td>
<td>6.22375</td>
<td>81.7763</td>
<td>12.0000</td>
<td>26.98 ± 0.82</td>
<td>54.36 ± 0.88</td>
<td>69.21 ± 0.4</td>
<td>83.96 ± 0.28</td>
</tr>
<tr>
<td>5</td>
<td>3.00000</td>
<td>72.3401</td>
<td>24.6599</td>
<td>14.22 ± 1.29</td>
<td>37.49 ± 1.88</td>
<td>54.44 ± 2.37</td>
<td>76.92 ± 3.24</td>
</tr>
<tr>
<td>6</td>
<td>4.85184</td>
<td>67.6804</td>
<td>27.4677</td>
<td>21.98 ± 0.98</td>
<td>51.42 ± 2.15</td>
<td>69.33 ± 2.45</td>
<td>95.57 ± 0.08</td>
</tr>
<tr>
<td>7</td>
<td>7.00000</td>
<td>55.0000</td>
<td>38.0000</td>
<td>55.54 ± 0.4</td>
<td>80.26 ± 0.04</td>
<td>100 ± 0</td>
<td>96.45 ± 2.01</td>
</tr>
</tbody>
</table>

*Indicates the average responses of duplicate experimentation.
**In-vivo pharmacokinetic study**

Experimental design was adopted for the evaluation of pharmacokinetics parameters of the optimized formula (CNZ emulsion gel calcium pectinate beads) compared to the commercially available immediate release tablets Stugeron® containing 25 mg CNZ (reference product) after single administration. Six healthy human volunteers were employed in the study, and none of them were on treatment 1 week before the study. The study was fully explained to the volunteers before being carried out. The study followed the ethics for treatment of human volunteers approved by Cairo University Ethical Committee. An informed consent was signed by each volunteer after they had understood the aim of their participation in the study.

The study was performed on two periods. Period I: Stugeron® tablets were administrated by three human volunteers (group I), the other three human volunteers (group II) administered optimized CNZ calcium pectinate beads equivalent to 25 mg CNZ. Twelve hours fasting with free access to water was demanded from the human volunteers. The volunteers administered the formulae orally with 200 ml water. A wash out period of 1 week separated the two periods. Period II: the two groups were interchanged.

Blood samples (5 ml) for assay of plasma concentrations of CNZ were obtained via the indwelling cannula immediately prior to dosing and at the time of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0 and 24 h after oral administration. Heparinated polyethylene tubes were used and were centrifuged immediately at 3000 rpm for 5 min. The plasma obtained was frozen at −20°C in labeled polypropylene tubes till LC-MS/MS analysis. LC-MS/MS method for quantitative determination of CNZ was previously described by the author’s in another work (Abouelatta et al., 2015). Briefly, plasma concentrations of CNZ were analyzed using a validated LC-MS/MS method. LC system (Agilent 1260®, Germany) coupled with triple quadrupole MS/MS detector (Agilent 6410®, Germany) was used. The chromatographic separation was carried out on a C18 Poroshell® 120, 4.6 × 50 mm, 2.7 µm. The mobile phase was composed of 10 mM ammonium acetate pH 3.3: acetonitrile [35:65] (v/v). The flow rate was set as 0.4 ml/min, and sildenafil was used as an internal standard (Abouelatta et al., 2015).

After oral administration of the two treatments of CNZ, pharmacokinetic parameters were determined from plasma concentration time profiles by means of non-compartmental analysis using Kinetica® (version 5, Thermo Fischer Scientific, Waltham, MA). Maximum CNZ concentration (Cmax, ng/ml) and the time required to reach maximum CNZ concentration (Tmax, h) were obtained from the individual plasma concentration time curves. The elimination rate constant (K, h⁻¹) was obtained from the slope of the linear regression of the log-transformed plasma concentration–time data in the elimination phase. Elimination half-life (t1/2, h) was calculated from the formula 0.693/K. The area under the plasma concentration–time curve (AUC0 to ∞) was subdivided into AUC0 to 24 (determined as the area under the plasma

<table>
<thead>
<tr>
<th>Table 4. The selected equations describing each response of floating CNZ emulsion gel calcium pectinate beads.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
</tr>
<tr>
<td>Y1: (Percent of drug released after 1 h)</td>
</tr>
<tr>
<td>Y2: (Percent of drug released after 5 h)</td>
</tr>
<tr>
<td>Y3: (Percent of drug released after 8 h)</td>
</tr>
<tr>
<td>Y4: (Percent of loading efficiency)</td>
</tr>
</tbody>
</table>

Figure 1. In-vitro release profile of CNZ from emulsion gel calcium pectinate beads formulae in 0.1 N HCL.
concentration–time curve up to the last measured sampling time and calculated by the linear trapezoidal rule) and area under the curve from \( C_t \) to infinity (AUC\(_{t \to \infty}\)); where AUC\(_{0 \to \infty}\) = AUC\(_{0 \to 24}\) + \( C_t / K \) (\( C_t \) is the last sample concentration at time \( t \)).

The pharmacokinetic parameters (\( C_{\text{max}}; \text{AUC}_{0-24} \) and \( \text{AUC}_{0-\infty} \)) of the optimized CNZ-loaded emulsion gel calcium pectinate beads and the reference treatment (Stugeron\(^\text{®}\)) were compared statistically using ANOVA with a level of significance of 0.05, and a \( p \) value smaller than 0.05 was considered significant.

Results and discussion

Analysis of the D-optimal mixture design

D-optimal mixture design can be considered as a tailored form of classic mixture designs. These designs are more robust to constraints and can produce complex designs with many design constraints. Correlation between effect estimates can be adopted by D-optimal design, and this shows the difference between standard and classical design of experiments (factorials and fractional factorials) and D-optimal design matrices (Lewis et al., 1999). The Minitab\(^\text{®}\) software
version 16.1.1) suggested seven formulae prepared in duplicate. The observed responses are recorded in Table 2. The observed responses (Y₁, Y₂, Y₃ and Y₄) were fitted to the previously mentioned models (Linear, Quadratic or special cubic) as shown in Table 3, and the model is selected according to the lowest predicted sum of squares (PRESS). The equations fitting each of the studied factors (A, B and C) to the observed responses (Y₁, Y₂, Y₃ and Y₄) according to its preferred model are shown in Table 4.

The release of CNZ from oil entrapped emulsion gel calcium pectinate beads was observed to vary depending on the composition of each batch as shown in Figure 1. It was clearly found that some formulations showed biphasic release.
pattern characterized by an initial burst release 52.62% in half an hour followed by gradual slow release to reach 100% after 8 h. On contrary to that, some formulations showed gradual release varying from 7.28 to 16.16% in the first half an hour of release and reached up to 70% CNZ released after 8 h. The 3D surface plot in Figure 2 showed that the percent of drug released after 1 h ($Y_1$) had followed the quadratic model, whereas the percent of drug released after 5 and 8 h ($Y_2$ and $Y_3$) was found to follow the linear model as shown in Table 4. The percent of pectin (A) in the formula played an antagonistic role on the amount of CNZ loaded. On the other hand, increasing the amounts of the oily phase (GMO and LL) (B and C), the percent of CNZ loaded was increased; thus, a synergistic effect was observed. The previously mentioned observations might be due to increased pectin where Ca$^{2+}$ in CaCl$_2$ solution became saturated causing pre-gelation, a rapid reaction between pectin molecules and calcium ions, resulting in non-homogeneous gel structure (Pawar et al., 2008). On the other hand, wetting of drug particles with the liquids having lipid nature (GMO and LL) enhanced drug loading (Patel et al., 2012).

**Optimization**

The aim of the optimization of pharmaceutical formulations is generally to determine the levels of the variable from which a robust product with high-quality characteristics may be produced (Basalious et al., 2010). The Minitab® software (version 16.1.1) automatically suggested one optimum formula after correlating both dependant and independent factors based on desirability function. The suggested optimized formula was characterized to have zero-order release profile for 12 h with maximum loading efficiency. Table 5 shows the constraints used in the optimization process.

As shown in Table 5, the optimized formula values were 3.28% LM-pectin (A), 70.54% GMO (B) and 26.17% Labrafac Lipophile (C).

A check point batch was prepared according to the predetermined software values. The release profile for the check point batch was compared to the target release profile as shown in Figure 4. Minimum residual was observed between both the expected and the observed values of the studied responses as shown in Table 5. Therefore, the previously mentioned results indicate the validity of the design.

**Swelling index**

The swelling of CNZ-loaded calcium pectinate beads was carried out in 0.1 N HCl. SI is represented in Figure 5 and Table 6. It was observed that on increasing the percent of pectin in the formula, the SI was decreased. This could be attributed to the protonation of pectin at acidic pH forming an insoluble form of minimum swelling (Badve et al., 2007).
Morphological examination and SEM

The photo of emulsion gel calcium pectinate beads loaded with CNZ showed that the beads were white, translucent and almost spherical after drying. The beads become somehow less spherical as a result of gradual water diffusion during drying as shown in Figure 6. SEM micrographs at different magnification powers were shown in Figure 7 for the optimized CNZ-loaded calcium pectinate beads. CNZ emulsion pectinate beads are almost spherical with smooth external surface. On further magnification, an intact smooth surface was observed as well as pores on the surface were noticed which might be representing the oil droplets (Sriamornsak et al., 2004).

After 8 h release, SEM micrographs showed sponge-like structure corresponding to the egg-box model which is rigid and water insoluble (Sriamornsak et al., 2004). On magnification, the external surface showed honey-comb-like structure with large wide pores which might be due to swelling of the beads in the release media, and these pores were suggested to be the way through which the drug was released into the media.

Floating time (floating behavior)

The emulsion gel calcium pectinate beads could float immediately with no lag time and remained floating for 8 h (Sriamornsak et al., 2008) as shown in Figure 8. The beads floated with an oil amount of 30% (w/w). It was observed that GMO swelled in water and the swollen mass floated for a prolonged period of time (Kumar et al., 2004). Good in-vitro floating behavior in 0.1 N HCl was observed. The floating properties of the emulsion gel beads may be attributed to the low-apparent density of the beads containing oils (Sriamornsak et al., 2004). This implied that the beads will have the tendency to exhibit a good in-vivo floating effect (Sriamornsak et al., 2008).

In-vivo pharmacokinetic study

Chromatograms showing blank human plasma and optimized CNZ-loaded emulsion gel calcium pectinate beads after oral administration are attached in Figures 9 and 10. Mean plasma concentrations of CNZ-time curves achieved after single administration of both Stugeron® 25 mg, and the optimized
Figure 8. CNZ-loaded calcium pectinate beads in 0.1 N HCL at zero time, after 4 and 8 h.

Figure 9. LC-MS/MS chromatograms of blank human plasma.
Figure 10. LC-MS/MS chromatograms of human plasma after oral administration of CNZ optimized formula.

Figure 11. Plasma concentration–time curve of Stugeron® tablets and optimized CNZ emulsion-loaded calcium pectinate beads.
calcium pectinate emulsion gel beads equivalent of 25 mg CNZ is shown in Figure 11. Table 7 clarifies the pharmacokinetic parameters following the oral administration of both formulae. Optimized CNZ-loaded emulsion gel calcium pectinate beads showed that there was significant difference $\left( p<0.05 \right)$ in case of $\text{AUC}_0\text{t} \rightarrow \infty$ compared to the commercially available Stugeron tablets, while insignificant difference $\left( p>0.05 \right)$ was declared in case of $\text{C}_{\text{max}}$, $\text{T}_{\text{max}}$ and $\text{AUC}_0\text{t} \rightarrow 24$.

The mean $\text{AUC}_0\text{t} \rightarrow 24$ and the $\text{AUC}_0\text{t} \rightarrow \infty$ of the optimized CNZ-loaded emulsion gel calcium pectinate beads was found to be 1.79 and 3.80 times that of Stugeron tablets, respectively. The increased $\text{C}_{\text{max}}$ and higher AUC indicate a slow and prolonged release of the optimized CNZ-loaded emulsion gel calcium pectinate beads formula with higher bioavailability in comparison with the commercially available Stugeron tablets. According to the previously mentioned results, the optimized CNZ-loaded emulsion gel calcium pectinate beads offered in-vivo prolonged release for CNZ over 12 h with higher bioavailability compared to once daily administration of commercially available Stugeron tablets. On increasing residence of CNZ in the acidic medium of the stomach, gradual release of CNZ in the stomach was observed leading to increased bioavailability of the drug and prolonged plasma concentration profile.

**Conclusion**

The achieved optimized CNZ emulsion gel calcium pectinate beads were suggested to be a selected candidate for continuous delivery of CNZ in the stomach that would be potentially suitable for once daily administration, with excellent floating properties, high-loading efficiency and zero-order release pattern. A promising in-vivo CNZ controlled release dosage form with higher bioavailability, when compared to once daily administration of Stugeron tablets, was achieved.

**Acknowledgements**

The authors would like to thank PharmaSolutions Research Center, Cairo, Egypt, for performing the in-vivo study section.

**Declaration of interest**

The authors report no declaration of interest. Only the authors are responsible for the content and writing of this paper.

Table 7. Mean pharmacokinetic parameters of Stugeron® tablets and optimized CNZ calcium pectinate beads.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Stugeron® tablets</th>
<th>Optimized CNZ emulsion gel calcium pectinate beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{C}_{\text{max}}$ (ng/ml)</td>
<td>41.34</td>
<td>73.89</td>
</tr>
<tr>
<td>$\text{T}_{\text{max}}$ (h)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>$\text{AUC}_0\text{t} \rightarrow 24$ (ng h/ml)</td>
<td>292.35</td>
<td>524.13</td>
</tr>
<tr>
<td>$\text{AUC}_0\text{t} \rightarrow \infty$ (ng h/ml)</td>
<td>307.19</td>
<td>1165.88*</td>
</tr>
<tr>
<td>$\text{T}_{1/2}$ (h)</td>
<td>5.76</td>
<td>32.46</td>
</tr>
<tr>
<td>$K$ (h$^{-1}$)</td>
<td>0.12</td>
<td>0.021</td>
</tr>
</tbody>
</table>

*Statistically significant $\left( p<0.05 \right)$.

**References**


Streubel A, Siepmann J, Bodmeier R. (2006). Drug delivery to the upper stomach, gradual release of CNZ in the stomach was observed leading to increased bioavailability of the drug and prolonged plasma concentration profile.

**Conclusion**

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