RESEARCH ARTICLE

# Design and characterization of hollow/porous floating beads of captopril for pulsatile drug delivery

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The present study was aimed to design and characterize hallow/ porous floating beads of captopril for pulsatile drug delivery for the treatment of hypertension. Captopril, an antihypertensive agent, is one of the most commonly prescribed drugs for the treatment of patients with hypertension and congestive heart failure. The floating pulsatile concept was applied to increase the gastric residence of the dosage form, having lag phase followed by a burst release. To overcome the limitations of the various approaches for imparting buoyancy, hollow/porous beads were prepared. A preliminary study was done for selection of the polymer (low methoxy pectin and gellan gum) combination. Based on the preliminary studies, an optimized concentration of polymers was selected for formulation design with varying the concentration of sodium bicarbonate. The obtained floating beads were studied for physical characterization, *in vitro* release, *in vivo* gamma-scintigraphy study and stability study. Formulation F1E floating beads had a porosity of 38.41% and hollow with bulk density <1. The entrapment efficiency for formulation F1E was 83.10%, and the particle size of the beads was 1.124 mm. The floating beads showed a two-phase release pattern, with initial lag time in acidic medium followed by rapid pulse release in the phosphate buffer medium with *in vitro* release of 96.77% for almost 8 h. The *in vivo* gastric residence of batch F1E was subjected to gamma-scintigraphy imaging on rabbits to determine the retention of drug (beads) for up to 6 h. This approach suggested use of hollow sodium bicarbonate microparticles as promising floating-pulsatile drug delivery systems for site- and time-specific release of antihypertensive drugs.

***Key words:*** *Captopril, floating-pulsatile drug delivery, gamma-scintigraphy, sodium bicarbonate*

## INTRODUCTION

A delivery system with a release profile that is characterized by a time period of no release (lag time) followed by a rapid and complete drug release (pulse release) can be called as an ideal pulsatile drug delivery system. A pulsatile delivery system provides one or more rapid release pulses at predetermined lag times or at specific sites, resulting in better absorption of the drug, and thereby providing a more effective plasma–concentration time profile.[1] Natural biodegradable polysaccharides like pectin, guar gum, chitosan, sodium alginate and gellan gum have been used in controlled drug delivery. Various approaches to induce buoyancy in cross-linked beads have been used.[2-4] The use of sodium bicarbonate as a buoyancy imparting agent to produce floating beads is the most simple among the various approaches, and has been attempted successfully by many workers.[5] Their floating property was based on the evolution of $CO_2$ when in contact with an acidic environment, followed by the ability of the polymer gel to entrap it, which decreases their density below 1. These beads have been used to achieve a prolonged gastric residence time for sustained release/stomach-specific drug delivery, providing an opportunity for both local and systemic drug actions.[6]

In cardiovascular disease, capillary resistance and vascular reactivity are higher in the morning, and

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decrease later in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to the state of hypercoagulability of the blood. Because of this reason, the frequencies of myocardial infarction and sudden cardiac death are more prone during the early morning. Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body.

Captopril, an antihypertensive agent, is one of the most commonly prescribed drugs for the treatment of patients with hypertension and congestive heart failure. It has been reported, however, that the duration of the antihypertensive action after a single oral dose of captopril is only 6–8 h; therefore, clinical use requires a daily dose of 37.5–75 mg to be taken three times. It is practically highly water soluble and the bioavailability is 70%. Thus, it belongs to class 1 of the Biopharmaceutical Classification System (BCS). Captopril has a relatively short elimination half-life (2 h).[7] Thus, there is a strong clinical need and market potential for a dosage form that will deliver captopril in a controlled manner to a patient needing this therapy, thereby resulting in better patient compliance.

Multiparticulate or multiple-unit systems offer various advantages over single-unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, relative merits of bioavailability, more consistent blood levels and reproducibility, and avoid all or none effect. The aim of this study was to design and characterize the hallow/porous floating beads of Captopril for pulsatile drug delivery for the treatment of hypertension.

## MATERIALS AND METHODS

### Materials

Low methoxy pectin (LMP) was obtained as generous gift sample from Krishna Pectins Pvt. Ltd., Jalgaon, India. Captopril was obtained as a generous gift sample from Medrich Pharmaceuticals Pvt. Ltd., Bangalore, India, sodium bicarbonate from Poona Chemical Laboratory, Pune, India; Gellan gum (GG) from SRL Chemicals Pvt. Ltd., Mumbai, India; calcium chloride from Loba Chem Pvt. Ltd., Mumbai, India; And all other chemicals used were of analytical grade.

### Methods

#### *Formulation of the captopril beads*

Preliminary studies for selection of polymer combination: Four formulations were prepared by varying the concentration of polymers, low methoxy pectin and GG in different ratios of 3:1, 2.5:1.5, 2:2 and 1.5:2.5, keeping the concentration of drug and floating agent constant, as shown in Table 1.

Evaluation parameters like drug entrapment efficiency and *in vitro* drug release for the formulated beads were done, and the promising polymer combination was selected on the basis of the above parameters for further study.

#### *Ionotropic gelation/bead formation*

Three hundred milligrams of pectin and 100 mg GG (3:1) were dissolved in 10 mL of deionized water and 25 mg of captopril and various amounts of sodium bicarbonate were uniformly mixed so that the ratio of polymer:sodium bicarbonate was as shown in Table 2. The dispersion was sonicated for 30 min (Servewell Instruments Pvt. Ltd., Bangalore, India) to remove any air bubbles. The resultant dispersion was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 80 mL of 3% w/v calcium chloride ($CaCl_2$) solution containing 10% acetic acid. The content was stirred at 100 rpm using a magnetic stirrer for 15 min. The beads were then filtered, washed three times with distilled water and subsequently oven-dried at 50°C for 4 h.[8]

### Characterization of the beads

#### *Particle size analysis and surface morphology*

Fifty floating beads were analyzed for their size distribution by optical microscopy. The mean diameter was determined by measuring the number of divisions covered by the beads using an ocular micrometer previously calibrated using a stage micrometer. The surface morphology was analyzed with a scanning electron microscope (JEOL JSM-6360 SEM) operated at an acceleration voltage of 10 kV.[9,10]

#### *Determination of drug entrapment efficiency*

Accurately weighed quantities (20 mg) of beads from each batch were placed in 100 mL phosphate buffer, pH 7.4, and mechanically agitated on a shaker at 200 rpm for 24 h. The resultant dispersions were filtered and analyzed spectroscopically at 201 nm. The percentage entrapment efficiency was calculated using the following equation:[11]

EE% = (Actual drug content in the beads / theoretical drug content) × 100

#### *Bead porosity and bulk density*

The bead porosity and bulk density were assessed using a mercury porosimetry (Autoscan 60 Porosimeter, Quantachrome Software, USA). The pressure was varied from 0 to 6000 psi. The mercury intrusion data were recorded and plotted against pressure, standard values for the contact and surface tension of mercury used.[12]

#### *In vitro floating property study*

The floating properties of the beads were evaluated using a USP XXIII type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India) filled with 900 mL of 0.1 N HCl (pH 1.2) containing 0.02% w/v Tween 80, with paddle at a rotational speed of 100 rpm. The temperature of the medium was maintained at 37°C ± 2°C. One hundred beads of each batch

**Table 1: Preliminary studies for selection of the polymer combination**

| Formulation code | Drug (mg) | LMP:GG | $NaHCO_3$ (mg) | $CaCl_2$ % (w/v) | Acetic acid 10% (v/v) (mL) |
|---|---|---|---|---|---|
| F1 | 25 | 3:1 | 100 | 3 | 8 |
| F2 | 25 | 2.5:1.5 | 100 | 3 | 8 |
| F3 | 25 | 2:2 | 100 | 3 | 8 |
| F4 | 25 | 1.5:2.5 | 100 | 3 | 8 |

**Table 2: Formulation code for the captopril-floating beads**

| Formulation code | Drug (mg) | LMP:GG | $NaHCO_3$ (mg) | $CaCl_2$ % (w/v) | Acetic acid 10% (v/v) (mL) |
|---|---|---|---|---|---|
| F1A | 25 | 3:1 | - | 3 | - |
| F1B | 25 | 3:1 | - | 3 | 8 |
| F1C | 25 | 3:1 | 150 | 3 | 8 |
| F1D | 25 | 3:1 | 200 | 3 | 8 |
| F1E | 25 | 3:1 | 250 | 3 | 8 |

were placed in the media. The floating ability was observed visually.[13,14]

### *In vitro drug release*

The *in vitro* release studies[14] were performed in triplicate using a USP XXIII type I dissolution test apparatus (Electrolab TDT-06P). The dissolution media of 900 mL was filled in a dissolution apparatus and the temperature of the medium was set at 37°C ± 2. Beads equivalent to 50 mg of captopril were placed in each dissolution vessel and the rotational speed of the basket was set at 100 rpm. The study was carried out in 0.1 N HCl initially for 2 h (Batch F1A and F1B) and 6 h (Batch F1C to FIE), and followed with dissolution in phosphate buffer, pH 7.4. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through a muslin cloth, the concentration of captopril was determined spectrophotometrically (UV spectrophotometer; Shimadzu UV-1700 Pharmaspec, Tokyo, Japan) at 201 nm for the acidic and basic buffers.

### *In vivo studies (gamma-scintigraphy studies)*

#### Preparation of labeled beads

Radiolabeled beads of pectin (3%w/v) containing $TC^{99}O^-_4$ eluted from the generator ($TC^{99}$m Generator; Saxion Biotech Pvt. Ltd., Delhi, India.) and stannous chloride solution were prepared by the ionotropic cross-linking method described for batch F1E. The labeling efficiency of the process was determined by comparing the radioactive counts obtained from the separated wet beads with the total radioactive count of the initial radiolabeled pectin solution.[15]

#### Gamma image collection

The *in vivo* gastric residence of the beads of batch F1E was studied by gamma-scintigraphic images. Three adult male New Zealand white rabbits weighing approximately 2–2.5 kg were used for the study. After fasting for 24 h, the rabbits were allowed free access to food pellets (Chakan Oil Mills, Pune, India) and water for 12 h just before starting the study. The investigation was prepared according to form B of the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The radiolabeled beads of the F1E batch equivalent to 50 mg captopril were administered through a plastic tube directly in the stomach with the aid of 3–4 mL of water, using a syringe to push the beads forward. Gamma-scintigraphy was employed to measure the gastric transit rate with a GE gamma camera (Model Millennium MPT, Israel); posterior images of the rabbits were collected using a collimator, and about 1000 counts/s were collected. The gamma-scintigraphic imaging was taken immediately after the first dosing and was carried out for 6 h at specified time intervals under the dynamic planer conditions.

### *Stability study*

To assess the short-term stability, the optimized captopril beads were stored at 40°C/75% relative humidity (RH) for 3 months. After 30 days, 60 days and 90 days, the formulations were observed for change in physical appearance, % entrapment efficiency and drug release profile. Stability studies were performed according to ICH guidelines.[16]

## RESULTS AND DISCUSSION

### Formulation of the floating calcium pectinate beads

Based on the results of the preliminary studies, F1 formulation was selected for further studies because it showed the highest entrapment efficiency of 81.07% and highest *in vitro* drug release of 82.8% within 8 h.

Five formulations (F1A, F1B, F1C, F1D and F1E) of the captopril beads were formulated. Different concentrations of sodium bicarbonate were used as a gas-generating agent for formulations F1C, F1D and F1E, as shown in Table 2. The method used to prepare the calcium pectinate beads was by the dripping method using a 23-gauge needle into the 3% calcium chloride solution containing 10% v/v acetic acid. The beads were formed due to the cross-linking of the pectin with divalent calcium ions of the $CaCl_2$ solution. The reaction between $NaHCO_3$ and acetic acid occurred, liberating $CO_2$ as gas bubbles, which was responsible for floating of the beads.

## Characterization of the beads

### *Particle size analysis and surface morphology*

The prepared beads were subjected to scanning electron microscopy (SEM), and are shown in Figure 1. The beads with no gas-forming agent for F1B were small, dense and flattened at the base with a wrinkled circumference, as shown in Figure 1a. The beads with higher gas-forming agent concentrations for F1E were very rough and poros, as shown in Figure 1b. The cross-sectional morphologies of the floating beads F1E showed large, closed pores present in the pectinate gel matrix, as shown in Figure 1c. The surface topography reveals that the beads were highly poros because of rapid escape of the carbon dioxide during formulation.

The sizes of the beads of all the five batches are shown in Table 3. The size of the beads was found to be 0.946, 0.980, 1.004, 1.065 and 1.124 mm for formulations F1A–F1E. The bead size was found to increase with an increase in the concentration of the gas-forming agent, which may be due to the pore formation in the polymer matrix.

The stronger alkaline microenvironment formed by higher sodium bicarbonate amounts may be responsible for softening of the pectin beads, leading to deformation under the force of the agitation.

### *Drug entrapment efficiency*

% drug entrapment in the beads includes drug entrapped within the polymer matrices. The values of total % entrapment efficiency of the drug were in the range of 62.92–83.10% for dried beads, as shown in Table 3.

The high entrapment efficiencies are seen with higher concentrations of gas-forming agent. Batch F1A, prepared in plain cross-linking solution, showed lower drug entrapment (62.92%) than the other batches having an acidified cross-linking solution. This may be due to decreased drug solubility in the acidic cross-linking solution. The effect of sodium bicarbonate can be attributed to the formation of an alkaline microenvironment inside the bead, enhancing the drug solubility combined with the effervescent action, giving rise to modifications of the bead matrix *in situ*.

In batch F1C, the less amount of sodium bicarbonate acted individually, causing scattered microchannels, leading to drug loss. For batch F1D and F1E, a collective action exerted by the increased amount of sodium bicarbonate led to the formation of prominent hollow structures due to entrapment of the generated gas. This entrapment leads to the coalescence of gas bubbles, which pushed the internal matrix toward the periphery, forming thick boundaries and, thereby, minimizing drug leaching.

### *Bead porosity and bulk density*

Porosity was studied to determine the effects of gas-forming agents on the pore structure of the floating beads. The % porosity for the formulations of F1C, F1D and F1E was 28.34, 32.12 and 38.41%, respectively. Increase in the porosity was observed from batches F1C, F1D and F1E by increasing the ratio of the gas-forming agent. Partial entrapment of carbon dioxide in the beads forming hollow areas and escaping of $CO_2$ led to porous structures in the matrix.

Bulk density of the beads ranges from 1.73±0.05 to

**Table 3: Physical characterization of the formulated beads**

| Formulation code | Particle size (mm)* | % entrapment efficiency* | Bulk density (g/cc) | Bead porosity (%) | Floating ability in 0.1 N HCl (h) |
|---|---|---|---|---|---|
| F1A | 0.946±0.058 | 62.92±1.02 | 1.73±0.05 | – | 0 |
| F1B | 0.980±0.069 | 70.27±2.52 | 1.42±0.17 | – | 0 |
| F1C | 1.004±0.068 | 72.0.±1.72 | 0.91±0.27 | 28.34 | 6 |
| F1D | 1.065±0.064 | 79.41±2.15 | 0.78±0.13 | 32.12 | 8 |
| F1E | 1.124±0.090 | 83.10±1.52 | 0.72±0.07 | 38.41 | 12 |

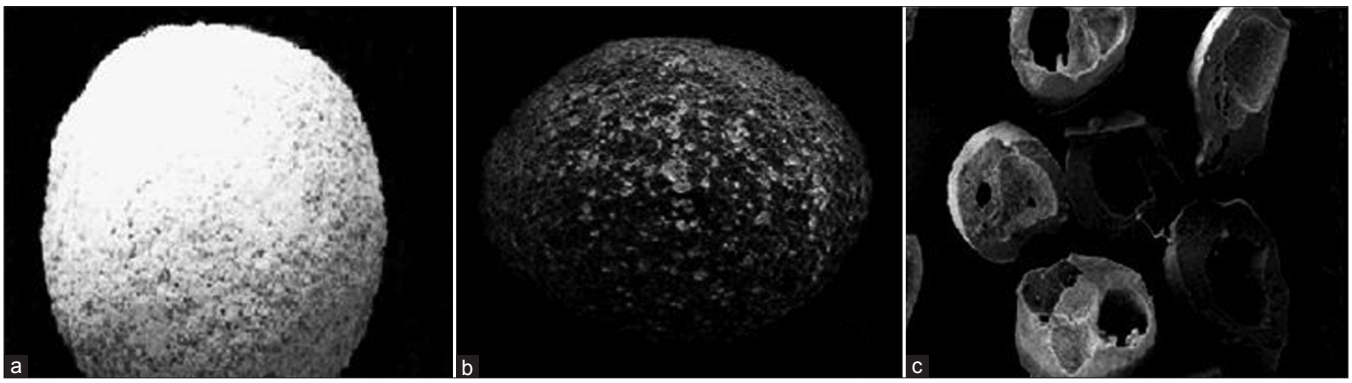


**Figure 1:** Scanning electron microscopy photographs of the captopril formulation beads

0.72±0.07 g/cc, as shown in Table 3. The bulk density of the hollow beads (F1C, F1D and F1E) was less as compared with the beads without sodium bicarbonate (F1A and F1B). The higher amount of effervescent agent caused faster and higher $CO_2$ generation. This may be attributed to a decrease in the bulk density.

### *Buoyancy test*

The floating ability of the prepared beads was evaluated in 0.1 N HCl as a dissolution medium. Buoyancy of the beads is directly related to the concentration of the gas-forming agent. As the concentration of the gas-forming agent increases, the number of air-trapped pores in the beads increases, which makes the beads to float. Beads of batch F1A and F1B were gas-forming agent-free beads, completely nonfloating and sunk immediately, whereas beads of batches F1C, F1D and F1E produced floating beads with a buoyancy lag time of 1 min and remained floating for 6 h, 8 h and 12 h, respectively [Table 3]. Instantaneous *in vitro* floating behavior was observed for the beads, which may be due to the low apparent density provided by the poros nature of the beads.

### *Drug release studies*

The dissolution study of all the formulations of the captopril beads was carried out in two different media, namely 0.1 N HCl and phosphate buffer pH 7.4.

The floating beads were considered to be gastroretentive for 6 h, making the basis for the *in vitro* dissolution time in acidic medium. All these beads released 10.60–15.07% of the drug in the acidic medium, irrespective of time.

Batch F1A and F1B showed 15.19 and 15.07% drug release within 2 h in acidic medium, while batch F1C, F1D and F1E showed 17.56, 12.74 and 10.60% drug release within 6 h in acidic medium, respectively. There was a slow release within 6 h. After 6 h, there was immediate pulse release within 30–45 min in phosphate buffer, and the remaining drug release was observed for about 3 h. Batches F1A, F1B, F1C, F1D and F1E showed 89.94, 88.92, 90.39, 92.24 and 96.77% drug release in phosphate buffer, as shown in Figure 2.

The poros beads showed excellent lag in drug release at acidic pH, which may be due to the insolubility of pectin. GG has the maximum sustaining effect in the acidic medium. At acidic pH, calcium pectinate and GG remains protonated into an insoluble form with reduced swelling. The second phase of the pulsed release in pH 7.4 can be attributed to rapid swelling and gel relaxation of calcium pectinate and GG at alkaline pH. Secondly, at pH >6.6, captopril is freely soluble, which resulted in rapid and complete drug release.

### *In vivo studies*

The *in vivo* gastric residence of batch F1E was studied by gamma-scintigraphy images of radiolabeled beads using rabbit as the animal model. In the stomach, the insoluble beads acted as indigestible food particles. The representative gamma images obtained of a rabbit are shown in Figure 3. It can be interpreted from the images that the beads were clumped together to give a discrete bright spot, which can be seen from the images up to fourth hour. After that, the mass started to diffuse to some extent in the gastric content up to the end of the sixth hour in the period of the study.

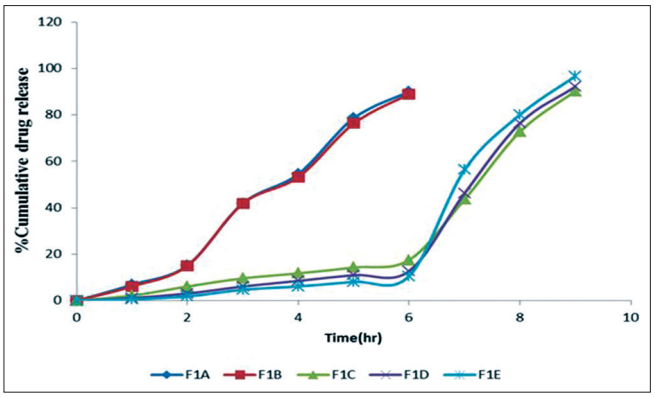


**Figure 2:** *In vitro* release profile for formulations F1A, F1B, F1C, F1D and F1E

### *Stability studies*

A stability study was conducted for the prepared beads of formulation F1E at a temperature of 40°C and 75% RH.

The % entrapment efficiency after 30, 60 and 90 days of exposure was found to be 82.42, 80.84 and 80.11, respectively. The percentage drug release for the same formulation after 30, 60 and 90 days of exposure was found to be 96.92, 95.72 and 94.85, respectively. On comparing it with the initial data of % entrapment efficiency (83.1) and cumulative % drug release (96.77), there was not much change in the % entrapment efficiency and cumulative % drug release. Thus, the results indicated that the bead formulation was stable at a temperature of 40°C and 75% RH.

## CONCLUSION

The hollow beads containing captopril showed excellent buoyancy in the acidic environment of the stomach. The enhanced buoyancy of the poros beads makes them excellent candidates for intragastric floating drug delivery by slowing down the gastric emptying. Pulsatile drug delivery was characterized by rapid and complete drug release from the drug-loaded poros beads due to the fast disintegration in the buffer of pH 7.4 after a lag time in an acidic environment. The release from poros beads was due to faster entry of the gastrointestinal fluid through the weak matrix and faster rupturing of the bead in the buffer. Overall, the buoyant beads provided a lag phase while showing gastroretention, followed by a pulsatile drug release that would be beneficial for hypertension.

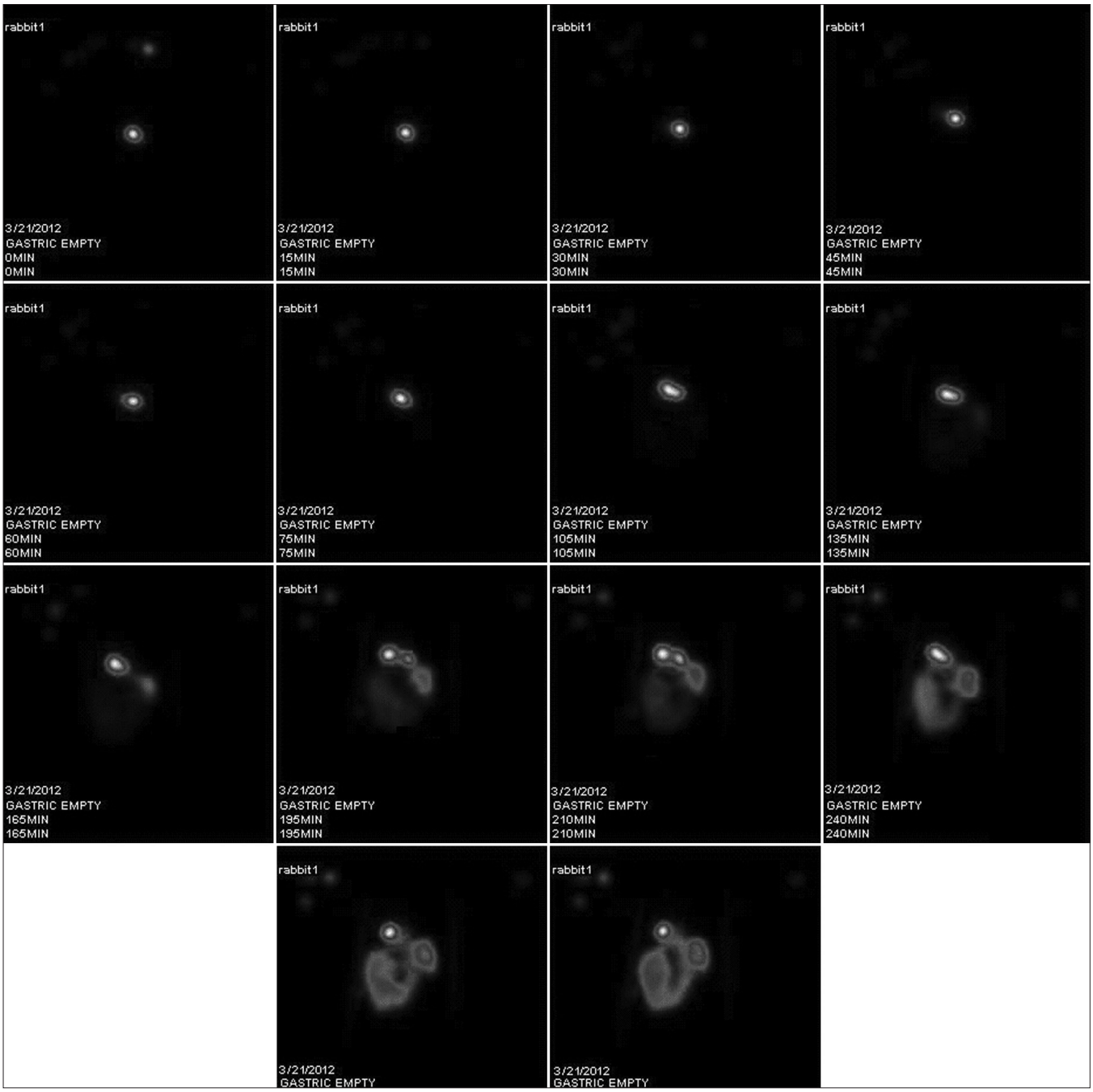


**Figure 3:** Gamma-scintigraphic images of the captopril-loaded calcium pectinate beads (F1E) in rabbits

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