Polysaccharides are widely used in oral drug delivery systems because of the simplicity to obtain the desired drug delivery system and drug release profile, by the control of cross-linking, insolubility of crosslinked beads in gastric environment and broad regulatory acceptance. They include sodium alginate, pectin, chitosan, xanthan gum, guar gum, starch, dextran, gellan (1–5). Among their various applications, polysaccharides are used for oral controlled release matrices, floating or bioadhesive sustained release beads or tablets, enteric coating, colon targeting of drugs and for pulsatile drug release (6–9). Pectin is an important ionic polysaccharide found in the plant cell wall, chemically made up of linear chains of partially methylated galacturonic acid units with an overall

The purpose of this study was to improve the entrapment efficiency of the water-soluble drug metronidazole using internal cross-linking agents. Calcium pectinate beads containing metronidazole were prepared by dropping a drug-pectin solution in 1% and 5% (m/V) calcium chloride for surface cross-linked beads. For the core cross-linked beads calcium carbonate was dispersed in the drug-pectin solution. The beads were characterized by particle size, swelling ratio, SEM, DSC, and in vitro drug release. It was found that the beads obtained by core cross-linking produced more drug entrapped beads than the surface cross-linked beads. Beads obtained using 1% (m/V) calcium chloride showed more drug entrapment than these obtained using 5% calcium chloride. The core cross-linking of pectin beads reduced drug loss by about 10–20%. The water lodging capacity of beads depended upon gel strength which is a function of the internal gelling agent and pectin concentration. Complete drug release was observed within 30–60 min in the acidic dissolution medium. This work has showed that the core cross-linking agent increases the water-soluble drug entrapment in calcium pectinate beads.

Keywords: ionotropic gelling, core cross-linking agent, CaCO₃, entrapment, metronidazole, Ca-pectinate beads

Polysaccharides are widely used in oral drug delivery systems because of the simplicity to obtain the desired drug delivery system and drug release profile, by the control of cross-linking, insolubility of crosslinked beads in gastric environment and broad regulatory acceptance. They include sodium alginate, pectin, chitosan, xanthan gum, guar gum, starch, dextran, gellan (1–5). Among their various applications, polysaccharides are used for oral controlled release matrices, floating or bioadhesive sustained release beads or tablets, enteric coating, colon targeting of drugs and for pulsatile drug release (6–9). Pectin is an important ionic polysaccharide found in the plant cell wall, chemically made up of linear chains of partially methylated galacturonic acid units with an overall

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molecular mass of 20,000 to 400,000. Calcium ions are essential for gelation of low methoxyl pectin, which is determined by the degree of esterification and the degree of amidation. Degrees of esterification and amidation determine the gelling behavior of pectin. Degrees of esterification, amidation and exact arrangement of acid and methyl ester groups along the pectin molecule control how the pectin behaves as a gelling agent. The extent and rate of cross-linking depend on the valency of cross-linking agent, molecular size of the drug and concentration of the cross-linking agent as well as on the speed and curing time during processing (10–12). Solubility, molecular size and ionic nature of the drug determine the drug entrapment and drug release. The water soluble and low molecular mass drugs have poor entrapment compared to insoluble and large molecular mass drugs (13–15).

The drug entrapment and drug release may be governed by the extent of surface and core cross-linking of beads, as a function of cation penetration into the bead, molecular size of the drug and valency of the cross-linking agent. Beads formed with closely packed polymer arrangement and egg-box or three-dimensional bonding may have different drug holding and releasing abilities. Low methoxyl-pectins (< 40% esterified) gel by calcium di-cation bridging between adjacent two-fold helical chains forming the so-called egg-box junction zone structures as long as a minimum of 14–20 residues can cooperate. Inclusion of the internal cross-linking agent may be effective for structuring bead core and thus enhancing the entrapment efficiency of the water-soluble drug (16, 17).

The purpose of the present work was to study the effect of core and surface cross-linking of pectin beads on the entrapment efficiency of metronidazole, beads swelling and drug release. CaCO₃ and CaCl₂ solutions were used as core and surface cross-linking agent, respectively. Metronidazole (MZ), a low molecular mass, water-soluble drug, widely used as an anti-amoebic, anti/protozoal and for prevention of recurrence of peptic ulcer disease caused by *H. pylori*, was selected as the model drug.

**EXPERIMENTAL**

**Materials**

Pectin (LM-104 AS) was a generous gift from CPKelco Pvt. Ltd. (India). Metronidazole was donated by Aarti drugs Ltd. (India). Calcium chloride was purchased from Sisco Research Lab. Pvt. Ltd. (India). All other chemicals used were of analytical reagent grade.

**Procedures**

Preparation of core and surface cross-linked beads – Pectin solutions of different concentrations were prepared by dissolving low methoxyl (LM) pectin in water under gentle agitation (Table I). Metronidazole (400 mg) was dispersed in 10 mL of the pectin solution under constant stirring for 2 min for uniform distribution. The resultant dispersion was extruded dropwise through a 1.2-mm diameter needle into 60 mL of stirred calcium chloride solution of 1% and 5% (m/v) at room temperature. The extrusion flow rate was approximately 4 mL min⁻¹, and then the beads formed were allowed to remain in the
stirred solution for 10 min curing time. The beads were filtered and washed with 20 mL of distilled water, the absence of free metronidazole was observed in higher pectin concentration beads dried at room temperature for 24 hours. Such beads are named surface cross-linked beads.

Surface cross-linked beads containing an internally dispersed cross-linking agent were prepared by dispersing 400 mg of metronidazole and 10 mg of calcium carbonate in pectin solutions. The remaining process was as described for surface cross-linked beads. Though such beads have surface as well as internal cross-linking, for convenience they are termed core cross-linked beads. The beads prepared by the same procedure without drug are named placebo beads.

**Table I. Entrapment efficiency of core and surface cross-linked beads**

<table>
<thead>
<tr>
<th>Batch</th>
<th>Pectin concentration (%)</th>
<th>Internal gelling agent (CaCO₃) (%)</th>
<th>Encapsulation efficiency (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>EEdiff (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG3</td>
<td>3</td>
<td>0</td>
<td>38.4 ± 1.2</td>
<td>39.5 ± 1.1</td>
</tr>
<tr>
<td>AG3 (I)</td>
<td>3</td>
<td>0.1</td>
<td>62.5 ± 1.1</td>
<td>59.6 ± 1.2</td>
</tr>
<tr>
<td>AG5</td>
<td>5</td>
<td>0</td>
<td>70.4 ± 2.1</td>
<td>55.0 ± 1.0</td>
</tr>
<tr>
<td>AG5 (I)</td>
<td>5</td>
<td>0.1</td>
<td>86.1 ± 1.5</td>
<td>74.3 ± 3.1</td>
</tr>
<tr>
<td>AG6</td>
<td>6</td>
<td>0</td>
<td>75.7 ± 1.9</td>
<td>56.2 ± 3.3</td>
</tr>
<tr>
<td>AG6 (I)</td>
<td>6</td>
<td>0.1</td>
<td>89.3 ± 2.4</td>
<td>88.0 ± 2.7</td>
</tr>
<tr>
<td>AG7</td>
<td>7</td>
<td>0</td>
<td>79.4 ± 1.7</td>
<td>64.9 ± 2.2</td>
</tr>
<tr>
<td>AG7 (I)</td>
<td>7</td>
<td>0.1</td>
<td>90.8 ± 1.6</td>
<td>89.2 ± 2.3</td>
</tr>
<tr>
<td>AG8</td>
<td>8</td>
<td>0</td>
<td>88.2 ± 1.5</td>
<td>67.0 ± 1.9</td>
</tr>
<tr>
<td>AG8 (I)</td>
<td>8</td>
<td>0.5</td>
<td>93.9 ± 1.0</td>
<td>92.4 ± 0.1</td>
</tr>
</tbody>
</table>

EEdiff: Encapsulation efficiency difference.
<sup>a</sup> Mean ± SD, <i>n</i> = 3.

Surface cross-linked beads containing an internally dispersed cross-linking agent were prepared by dispersing 400 mg of metronidazole and 10 mg of calcium carbonate in pectin solutions. The remaining process was as described for surface cross-linked beads. Though such beads have surface as well as internal cross-linking, for convenience they are termed core cross-linked beads. The beads prepared by the same procedure without drug are named placebo beads.

**Particle size estimation**

The mean diameter of beads was determined using a stereomicroscope (Carl Zeiss, Germany) attached to a digital camera (Watec, Wat-202, Japan). The captured images were analyzed using the Biovis Image Plus software (Expert Tech Vision, India). About 20 particles of each batch were analyzed and the average diameter and different surface factors, such as circulatory factor, elongation, roundness and perimeter ratio, were determined.

**Encapsulation efficiency estimation**

The ratio of the actual metronidazole content in the drug-loaded beads to the theoretical metronidazole content was termed encapsulation efficiency. The total mass of dried beads obtained from a batch was considered as practical yield of the process.
Drug-loaded beads (100 mg) were dissolved in phosphate buffer pH 7.4 by shaking on a rotary shaker (Steelmet Industries, India) at 200 rpm overnight. The solution was filtered through a 0.45 μm pore size filter and, after sufficient dilution with phosphate buffer (pH 7.4), analyzed spectrophotometrically at 320 nm (Jasco V500, Japan). Determinations were made in triplicate.

Surface topography

The beads were mounted on standard specimen mounting stubs and coated with a thin gold-palladium layer (20 nm) in a sputter coater unit (VG Microtech, UK). Microphotographs of the beads were observed at 50× and 200× magnification using a Cambridge Stereoscan 120 scanning electron microscope (UK) operated at an acceleration voltage of 10 kV.

Differential scanning calorimetry (DSC)

Thermograms of metronidazole, calcium pectinate beads without drug and drug-loaded beads were obtained using a Mettler-Toledo DSC 821e (Switzerland) instrument equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale. Powder samples were hermetically sealed in perforated aluminum pans and heated at a constant rate of 10 °C min⁻¹ over a temperature range of 25–300 °C. The system was purged with nitrogen gas at the rate of 100 mL min⁻¹ to maintain inert atmosphere.

Swelling study

Swelling of the beads was studied in triplicate using three randomly selected beads from each batch. Beads of known mass were placed in the wire basket of a USP 26 type II dissolution apparatus (Electrolab TDT-06P, India) containing 900 mL of 0.1 mol L⁻¹ HCl (pH 1.2) maintained at 37 °C (18). The beads were periodically removed at predetermined time intervals during the study period of 2 hours, drained on tissue paper and weighed.

Dissolution studies

The dissolution of drug loaded calcium pectinate beads was studied using the USP 26 (18) type II dissolution test apparatus containing 900 mL of 0.1 mol L⁻¹ HCl (pH 1.2) maintained at 37 ± 0.5 °C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper, metronidazole concentration was determined spectrophotometrically at 320 nm. All the readings were done in triplicate. Data analysis was done using »PCP Disso v2.08« software (Poona College of Pharmacy, India).
Primary batches of drug-loaded pectin beads containing 3% (m/V) pectin produced satisfactory beads and this was selected as the minimum concentration for further studies. The 8% (m/V) pectin concentration was taken as the maximum pectin concentration, above which the solution was too viscous to drop. Aqueous solution of calcium chloride (1 and 5%) (m/V) was used as the surface cross-linking agent to compare relative calcium reactivity. Differences were observed in the encapsulation efficiency of thus formed batches. Encapsulation efficiency was in the range $38.4 \pm 1.2$ to $88.2 \pm 1.5\%$ as shown in Table I. The encapsulation efficiency of surface cross-linked beads increased with an increase in the pectin concentration but decreased with increasing the calcium chloride concentration from 1 to 5%. The calculated entrapment efficiency difference (EEdiff) was 14 to 21% except for batch AG3 containing the lowest polymer content. The increase in entrapment efficiency with an increase in pectin concentration at constant drug amount may be attributed to the availability of excess polymer to encapsulate the drug. The reduction in entrapment efficiency using 5% calcium chloride solution may be attributed to the weakening of surface gel strength due to an excess of Ca$^{2+}$ ions. The calcium concentration vs. gel strength curve reaches a point where further increase in calcium concentration does not increase the gel strength and this is indicated as calcium saturation. As calcium concentration continues to increase beyond this point, the gel strength decreases. This is caused by pre-gelation, a rapid reaction between pectin molecules and calcium ions, resulting in non-homogeneous gel structure (19, 20). The lower value of EEdiff for the 3% pectin containing batches can be correlated to the smaller amount of polymer and higher Ca$^{2+}$/polymer ratio.

Table II. Percent release profile of calcium pectinate beads at various time intervals

<table>
<thead>
<tr>
<th>Batch</th>
<th>Cross-linking agent</th>
<th>Release (%)a</th>
<th>1% CaCl₂</th>
<th>5% CaCl</th>
<th>10 min</th>
<th>30 min</th>
<th>60 min</th>
<th>10 min</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG3</td>
<td>CaCl₂</td>
<td>49.9 ± 4.2</td>
<td>75.5 ± 4.6</td>
<td>91.9 ± 1.5</td>
<td>53.5 ± 4.5</td>
<td>82.7 ± 4.6</td>
<td>92.0 ± 2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG3 (I)</td>
<td>CaCO₃</td>
<td>45.5 ± 3.3</td>
<td>67.1 ± 3.2</td>
<td>75.4 ± 2.5</td>
<td>42.9 ± 4.2</td>
<td>67 ± 4.25</td>
<td>83.6 ± 3.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG5</td>
<td>CaCl₂</td>
<td>61.4 ± 7.2</td>
<td>81.7 ± 8.1</td>
<td>86.2 ± 3.5</td>
<td>38.5 ± 2.5</td>
<td>80.0 ± 8.2</td>
<td>92.4 ± 4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG5 (I)</td>
<td>CaCO₃</td>
<td>48.4 ± 2.2</td>
<td>68.6 ± 1.8</td>
<td>73.9 ± 4.2</td>
<td>21.9 ± 3.6</td>
<td>60.5 ± 4.2</td>
<td>73.9 ± 3.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG6</td>
<td>CaCl₂</td>
<td>50.3 ± 2.5</td>
<td>73.6 ± 4.3</td>
<td>79.2 ± 6.2</td>
<td>44.1 ± 2.5</td>
<td>89.0 ± 4.2</td>
<td>96.6 ± 4.5</td>
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<tr>
<td>AG6 (I)</td>
<td>CaCO₃</td>
<td>21.5 ± 5.2</td>
<td>54.0 ± 2.6</td>
<td>65.3 ± 4.5</td>
<td>63.2 ± 4.2</td>
<td>72.5 ± 3.5</td>
<td>77.2 ± 6.2</td>
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<tr>
<td>AG7</td>
<td>CaCl₂</td>
<td>53.0 ± 7.6</td>
<td>78.2 ± 3.5</td>
<td>81.2 ± 3.3</td>
<td>35.9 ± 4.5</td>
<td>87.0 ± 2.5</td>
<td>93.3 ± 3.5</td>
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<td></td>
</tr>
<tr>
<td>AG7 (I)</td>
<td>CaCO₃</td>
<td>38.2 ± 5.1</td>
<td>56.5 ± 4.6</td>
<td>68.1 ± 2.4</td>
<td>43.7 ± 6.2</td>
<td>63.7 ± 1.2</td>
<td>68.5 ± 4.2</td>
<td></td>
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<tr>
<td>AG8</td>
<td>CaCl₂</td>
<td>65.3 ± 3.5</td>
<td>82.8 ± 5.3</td>
<td>85.6 ± 4.5</td>
<td>42.3 ± 4.2</td>
<td>83.5 ± 2.6</td>
<td>88.0 ± 4.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG8 (I)</td>
<td>CaCO₃</td>
<td>33.3 ± 2.8</td>
<td>60.7 ± 4.3</td>
<td>68.9 ± 4.3</td>
<td>36.9 ± 3.3</td>
<td>60.1 ± 3.5</td>
<td>67.1 ± 4.2</td>
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</table>

a Mean ± SD, n = 3.
The entrapment efficiency was further increased in batches containing calcium carbonate as the core/internal gelling agent. In the internally gelled batches containing 3% \((m/V)\) pectin, there was an almost 24 and 20% increase in entrapment efficiency using 1 and 5% \((m/V)\) calcium chloride, respectively. Internally gelled batches containing higher pectin concentrations, when compared to only surface cross-linked beads using 1% calcium chloride, showed improvement in drug entrapment in the range of 5 to 16% which reduced with decreasing pectin concentration. In the batches prepared using 5% calcium chloride, drug loss was markedly reduced by inclusion of the internal cross-linking agent (Table I).

This phenomenon may be a result of the physical and chemical interactions that can take place during the pectin gel bead formation. Pectin beads are formed by intermolecular cross-linking between divalent calcium ions and the negatively charged carboxyl group of pectin molecules. Divalent metals establish direct polyanion-cation-polyanion interaction between pairs of carboxylic groups on the neighboring helices producing an egg-box model. Weak and flexible gel turns strong and rigid as the cation availability increases with maximum gel strength for utilization of all possible cross-linking sites. When an excess of divalent cations is present, they compete for interaction with anionic sites, imposing repulsive forces resulting in weakening of gels (19). In surface cross-linked beads, the extent of \(\text{Ca}^{2+}\) interaction at the surface restricts further entry to the core, which is compensated by using an internal cross-linking agent, thereby increasing the bead strength and giving rise to increased dissolution/leaching of small and low molecular mass drug through the cross-linked network. This is supported by the high values of EEdiff, which can be attributed to the formation of soft gel due to the presence of excessive calcium ions.

The increase in drug entrapment and reduced values of EEdiff in internally gelled batches showed the dominance of internal cross-linking over the surface cross-linking. Intermolecular cohesion, which occurred during core cross-linking, might have counteracted the gel weakening, making both the core and surface closely compact. This is supported by reduced drug loss obtained with the 5% \((m/V)\) cross-linking solution. Keeping \(\text{CaCl}_2\) concentration constant, the increase in pectin concentration increased entrapment efficiency. This may be attributed to the corresponding increase in gel strength.

SEM photographs shown in Fig. 1 explain the surface morphology of dried metronidazole loaded Ca-pectinate beads. Beads prepared with 3% pectin solution with 1% calcium chloride showed prominent thin ridges by “pull-away” effect producing a rough surface, but beads prepared with the same pectin concentration using 5% CaCl2 solution were deformed with cavities on the surface (Figs. 1a, b). As compared to externally cross-linked beads, beads that were internally cross-linked with calcium carbonate and obtained by using 1 and 5% calcium chloride were spherical with entrapped drug crystals in thick gel (Figs. 1c, d). Figs. 1e and 1f show that the surface of beads containing the highest pectin concentration, with surface and core cross-linking, was comparatively smooth with both 1% and 5% \((m/V)\) calcium chloride solution in a low resolution of SEM. In high resolution, fine drug crystals appeared on the surface due to squeezing of the drug (as in Fig. 1g). The surface of the beads containing the core cross-linking agent showed fewer drug crystals (Fig. 1h) than beads obtained only by surface cross-linking this reconfirms that the reduced leaching of drug into the \(\text{CaCl}_2\) solution may be the reason for the increased encapsulation efficiency.
The mean particle size of the beads ranged between 2.073 ± 0.057 and 4.376 ± 0.075 mm. The beads obtained were also evaluated for the circulatory factor and roundness. The beads were spherical with the circulatory factor in the range of 1.2 to 2.0 and roundness in the range of 0.35 to 0.83. In surface cross-linked batches, the mean particle size of the beads containing a constant drug amount increased with the increase in polymer concentration. Increase in the calcium ion concentration decreased the gel strength of the beads; 5% calcium chloride increased bead size.

DSC thermograms of metronidazole, unloaded beads and drug loaded calcium pectinate beads of batch AG5 are shown in Fig. 2. Metronidazole showed melting endotherms at 160.79 °C (160.44–167.89 °C). Empty pectin beads had two melting endotherms and drug loaded beads had three endotherms because the drug showed its own characteristic peak. The broad endotherm at 90–115 °C in plain and drug loaded beads
may be due to water loss, the peak intensity of which decreases in internally cross-linked beads. Shifts of the drug melting endotherm to higher temperature were observed in internally cross-linked beads, which may be attributed to slower heat transfer with increase in bead hardness.

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**Fig. 2.** DSC thermograms of: a) metronidazole, b) empty Ca-pectinate beads, c) drug-loaded externally cross-linked beads, d) drug-loaded internally cross-linked beads (CaCO₃).

**Fig. 3.** Swelling ratio of Ca-pectinate beads: a) batch AG3; b) batch AG5 (mean ± SD, n = 3).
Internally cross-linked beads of AG3 (Fig. 3a) showed rapid swelling with the shortest steady state. This may be attributed to faster penetration of the fluid and erosion due to weak gel strength (Fig. 3b shows the batches containing a low pectin concentration). Maximum swelling was observed within 20 min. Swelling properties of the beads containing 5% pectin (AG5), high swelling ratio and slower erosion, indicated the optimum amount of pectin and Ca\textsuperscript{2+} concentration for cross-linking. The beads prepared with all concentrations of pectin solution showed a somewhat similar swelling profile with the swelling ratio around 2 and no erosion within 120 min. The beads obtained by internal cross-linking had a lower swelling capacity. A lower pectin concentration shows a higher swelling ratio, and vice versa.

All the beads showed almost 80% drug released within 30 to 60 min at pH 1.2. The drug release was dependent on drug solubility in dissolution medium, because the fluid migrates into the beads to dissolve the drug and create pores and channels. Fluid ingress promotes the extent and the rate of beads swelling, creating a large surface area, which in turn enhances the release of incorporated drugs. A typical drug release profile is shown in Fig. 4 and the cumulative release at different times is given in Table II. The initial drug release from beads prepared using 5% calcium chloride solution was slower than from that prepared using 1% calcium chloride. The delay in drug dissolution reveals that the internally cross-linked beads compact the core, which decreases the drug release from the core of the beads. Internal gelling increased gel strength by cross-linking in the core, increasing the drug holding capacity.

CONCLUSIONS

The pharmaceutical properties of the ionically cross-linked polysaccharide beads are not only determined by the concentration and valency of the cation but also by the uniform internal and external cross-linking. This study emphasized the use of internal cross-linking agents to obtain cross-linked calcium-pectinate beads, promising for improved drug entrapment, size and shape. This approach may be useful to achieve sustained release of water-soluble drugs. Further studies should be done using internal cross-linking agents of different valency and cross-linking capacity.
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REFERENCES


S A Ž E T A K

Utjecaj umrežavanja na udio metronidazola u pektinskih zrnčima

ATMARAM P. PAWAR, ANIL R. GADHE, PRABAKARAN VENKATACHALAM, PRAVEEN SHER
i KAKASAHEB R. MAHADIK

Svrha istraživanja bila je poboljšati udio vodotopljive ljekovite tvari metronidazola u pripravcima s pektinskih zrnčima koristeći sredstva za umrežavanje poput kalcijevog karbonata. Površinski umrežena zrnca kalcijevog pektinata s metronidazolom pripravljena su dokapavanjem otopine lijeka i pektina u 1 i 5% (m/V) otopinu kalcijevog klorida. Zrnca s umreženom jezgrom pripravljena su dispergiranjem kalcijevog karbonata u otopinu lijekovite tvari i pektina. Zrnca dobivena umrežavanjem tekuće sadržavala su veći udio lijeka (10-20%) od površinski umreženih zrnaca. Zrnca dobivena s 1% (m/V) otopinom kalcijevog klorida sadržavala su veći udio lijeka od onih dobivenih s 5% otopinom. Kapacitet vezanja vode zrnca ovisio je o jakosti gelisa, a jakost gelisa ovisila je o internom agensu za geliranje i koncentraciji pektina. U kiselom mediju ljekovita tvar se u potpunosti oslobodila unutar 30-60 minuta.

Ključne riječi: ionotropsko geliranje, sredstvo za umrežavanje jezgre, kalcijev karbonat, udio lijeka, metronidazol, zrnca Ca-pektinata

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