Preparation and release characteristics of polymer-coated and blended alginate microspheres

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To prevent a rapid drug release from alginate microspheres in simulated intestinal media, alginate microspheres were coated or blended with polymers. Three polymers were selected and evaluated such as HPMC, Eudragit RS 30D and chitosan, as both coating materials and additive polymers for controlling the drug release. This study focused on the release characteristics of polymer-coated and blended alginate microspheres, varying the type of polymer and its concentration. The alginate microspheres were prepared by dropping the mixture of drug and sodium alginate into CaCl₂ solution using a spray-gun. Polymer-coated microspheres were prepared by adding alginate microspheres into polymer solution with mild stirring. Polymer-blended microspheres were prepared by dropping the mixture of drug, sodium alginate and additive polymer with plasticizer into CaCl₂ solution. In vitro release test was carried out to investigate the release profiles in 500 ml of phosphate buffered saline (PBS, pH 7.4). As the amount of polymer in sodium alginate or coating solution increase, the drug release generally decreased. HPMC-blended microspheres swelled but withstood the disintegration, showing an ideal linear release profiles. Chitosan-coated microspheres showed smooth and round surface and extended the release of drug. In comparison with chitosan-coated microspheres, HPMC-blended alginate microspheres can be easily made and used for controlled drug delivery systems due to convenient process and controlled drug release.

Keywords: Alginate, microspheres, HPMC, chitosan, polymer-coating, polymer-blending.

Introduction

Biopolymers are used as wall material in oral drug delivery systems because they are biodegradable, biocompatible and non-toxic. Sodium alginate and chitosan are commonly used biopolymers in the oral drug delivery system. Especially, sodium alginate has been commercially applied and investigated due to its low cost and minimal processing requirement. The use of sodium alginate for microencapsulation has been extensively studied for a long time.

Alginate is an anionic linear polysaccharide consisting of β-D-mannuronic acid (M-block) and α-L-guluronic acid (G-block) (Kikuchi et al. 1997). Sodium alginate is gelled when contacted with calcium ions in solution by crosslinking between the

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carboxylate anions of alginate guluronate units and the calcium ions (Kikuchi et al. 1997).


A variety of core materials such as drugs (Bodmeier and Wang 1992, Gürsoy et al. 1998, Acartürk and Takka 1999, Gürsoy and Ceviık 2000), proteins (Polk et al. 1993, Lemoine et al. 1998), dextran (Kikuchi et al. 1997), DNA (Quong and Neufeld 1999, Quong et al. 1999) and microorganisms (Jianlong et al. 1999, Cui et al. 2000) have been encapsulated in an alginate matrix.

Alginate microspheres are stable in acidic media but easily swell and disintegrate in alkaline media (Acartürk and Takka 1999). As calcium ions are being released by the ion exchange with sodium ions in the medium, electrostatic repulsion between the carboxylate anions further accelerates the swelling and erosion of alginate gels (Kikuchi et al. 1997). On account of short time release in alkaline media, alginate was not found to be an ideal sustained release wall material for microencapsulation. Therefore, there were many attempts to control the disintegration of alginate microspheres and extend the drug release.

Coating alginate microspheres with polycationic polymers such as chitosan (Murata et al. 1993, Hari et al. 1996, Rebeiro et al. 1999) or poly-L-lysine (Lemoine et al. 1998, Cui et al. 2000) has been commonly investigated for the controlled delivery of drug. Another technique involves blending polymers with sodium alginate to improve the diffusion properties of drug. Because there have been few published articles on polymer-blended alginate microspheres, polymer-blended alginate microspheres were prepared and investigated, varying the type and amount of additive polymer. Three polymers were selected and evaluated (HPMC, Eudragit RS 30D and chitosan) as both coating materials and additive polymers for controlling the drug release.

Felodipine was selected as a model drug for this research. Felodipine is a dihydropyridine derivative and an oral calcium channel blocker used for the treatment of hypertension (Abrahamsson et al. 1994, Gottfries et al. 1994, Acartürk and Sencan 1996). Felodipine is completely absorbed from the gut after oral intake, but the oral bioavailability of felodipine is low. (~15%) (Acartürk and Sencan 1996, Aberg et al. 1997). On account of these limitations, attempts were made to develop extended-release formulations for sustained absorption.

The objective was to prepare polymer-coated and blended alginate microspheres in order to control the drug release in simulated intestinal fluid. The study focused on the release characteristics of polymer coated and blended alginate microspheres, varying the type of polymer and its concentration.

**Materials and methods**

**Materials**

Felodipine was obtained from Nivedita chemicals PVT. Ltd (Mumbai, India). Eudragit RS 30D was purchased from Röhm (Darmstadt, Germany). Sodium alginate (low viscosity) and Hydroxy propyl methyl cellulose (HPMC) were purchased from Sigma (St Louis, MO, USA). Sodium alginate was derived from Macrocystis(Kelp) and the viscosity of sodium alginate solution (2% w/v)
was 80–250 cps at 20°C. The viscosity of 2% HPMC solution was 80–120 cps at 20°C. Chitosan and tween 80 (polyethylene sorbitan monooleate) were purchased from Showa Chemical Co. (Japan). The viscosity of 0.5% chitosan solution in 0.5% acetic acid was 5–20 cps, and degree of deacetylation was 75–85%. Methylene chloride was purchased from Samchun Chemical Co. (Korea). Calcium chloride was purchased from Yakuri Pure Chemical Co. (Japan). TEC (Tri Ethyl Citrate) was obtained from Junsei Chemical Co. (Japan).

**Preparation of plain alginate microspheres**

Alginate solution (100 ml) was prepared by dissolving sodium alginate (4% w/v) in distilled water with stirring. Two millilitres of tween 80 (2% v/v) was added as a surfactant. Felodipine (1 g) dissolved in methylene chloride (5 ml) was added to the above solution. The mixture in ice bath was homogenized at 8000 rpm for 10 min. The rpm was measured by Tachometer connected to the homogenizer (HMZ-20DN, Young-ji, Korea). The weight ratio between alginate and drug was 4:1. The mixture was prepared, poured into the inlet reservoir of spray gun and sprayed into a bath containing 5% CaCl₂ solution by a spray gun connected to air compressor (Euromatic Pro 550p, Youngwoo Fasteners Co.) maintaining at a constant air pressure. The alginate microspheres were cured for 30 min, filtered with a sieve and collected.

Figure 1 shows the preparation procedure of alginate microspheres. Plain alginate microsphere was expressed as control in this paper.

**Preparation of polymer-coated alginate microspheres**

Coating method involving organic solvents was avoided because felodipine is freely soluble in acetone and ethanol. Dipping method was used instead for coating microspheres in this experiment. HPMC, chitosan and Eudragit RS 30D coating solutions were prepared according to the formulation composition (table 1). TEC (40% w/w) was added to HPMC and Eudragit RS 30D solutions (100 ml) as a plasticizer and acetic acid (1% v/v) was added to the chitosan solution. The coating solutions were prepared with varying concentrations, as shown in table 1. The alginate microspheres were added to the polymer-coating solutions and stirred mildly with a magnetic bar for 20 min to evenly coat the surface of alginate microspheres. After coating, the microspheres were rinsed with distilled water, filtered and then dried for 8 h using a speed-vacuum drier at room temperature.

**Preparation of polymer-blended alginate microspheres**

Sodium alginate was dissolved in the distilled water (100 ml) with stirring. HPMC, Eudragit RS 30D or chitosan was added to the alginate solution and stirred to dissolve for 2 h. Chitosan and acetic acid (1% v/v) was added to the alginate solution. TEC (0.8 ml) was added as a plasticizer to improve the miscibility as well as the flexibility and plasticity of the resulting polymer. After adding TEC, this solution was stirred for 2 h. The ratio between alginate and polymer was varied, as shown in table 2. The prepared alginate polymer mixture was poured into the spray-gun as described above and sprayed into 5% CaCl₂ solution. Samples were dried and collected according to the preparation procedure for plain alginate microspheres.
Tables 1 and 2 show the formulation composition for the preparation of coating solution and polymer-blended alginate microspheres.

Size analysis

The average diameter of 15 dried microspheres was determined using a caliper (Mituyu, Japan).
Encapsulation efficiency

Microspheres (20 mg) were added in 100 ml of PBS, stirred for 24 h and then dissolved completely. A sample (1 ml) was withdrawn and analysed spectrophotometrically at 362 nm. The encapsulation efficiency was calculated from the theoretical amount of drug and actual amount of drug in dry microspheres.

Morphological analysis

Microspheres were mounted on metal grids using double-sided tape and coated with gold under a vacuum. Surface morphologies of microspheres were investigated with a Scanning Electron Microscope (SEM) (JSM-5310LV Scanning Microscope, Tokyo, Japan) at 25 kV.

Table 1. Formulation compositions for the preparation of coating solutions.

<table>
<thead>
<tr>
<th>Formulations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Polymer type</th>
<th>Polymer (g)</th>
<th>DW&lt;sup&gt;b&lt;/sup&gt; (g)</th>
<th>TEC&lt;sup&gt;c&lt;/sup&gt; (g)</th>
<th>AA&lt;sup&gt;d&lt;/sup&gt; (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC1</td>
<td>HPMC&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.5</td>
<td>100</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>HC2</td>
<td></td>
<td>1</td>
<td>100</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>HC3</td>
<td></td>
<td>2</td>
<td>100</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>EC1</td>
<td>Eudragit RS 30D</td>
<td>33.3</td>
<td>66.6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>EC2</td>
<td></td>
<td>66.6</td>
<td>33.3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>EC3</td>
<td></td>
<td>100</td>
<td>0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>CC1</td>
<td>Chitosan</td>
<td>1</td>
<td>100</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CC2</td>
<td></td>
<td>2</td>
<td>100</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CC3</td>
<td></td>
<td>4</td>
<td>100</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> HC: HPMC-coating; EC: Eudragit RS 30D-coating; CC: Chitosan-coating.

<sup>b</sup> DW: Distilled water.

<sup>c</sup> TEC: Tri ethyl citrate.

<sup>d</sup> AA: Acetic acid.

<sup>e</sup> HPMC: Hydroxy propyl methyl cellulose.

Table 2. Formulation compositions for the preparation of polymer-blended alginate microspheres.

<table>
<thead>
<tr>
<th>Formulations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Blending ratio</th>
<th>Alginate (g)</th>
<th>Polymer type</th>
<th>Polymer (g)</th>
<th>TEC (g)</th>
<th>DW (g)</th>
<th>AA (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB1</td>
<td>9 : 1</td>
<td>3.6</td>
<td>HPMC</td>
<td>0.4</td>
<td>0.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>HR2</td>
<td>8 : 2</td>
<td>3.2</td>
<td></td>
<td>0.8</td>
<td>0.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>HB3</td>
<td>7 : 3</td>
<td>2.8</td>
<td></td>
<td>1.2</td>
<td>0.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>EB1</td>
<td>9 : 1</td>
<td>3.6</td>
<td>Eudragit RS 30D</td>
<td>1.33</td>
<td>0.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>EB2</td>
<td>8 : 2</td>
<td>3.2</td>
<td></td>
<td>2.66</td>
<td>0.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>EB3</td>
<td>7 : 3</td>
<td>2.8</td>
<td></td>
<td>3.99</td>
<td>0.8</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>CB1</td>
<td>9.5:0.5</td>
<td>3.8</td>
<td>Chitosan</td>
<td>0.2</td>
<td>0.8</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>CB2</td>
<td>9 : 1</td>
<td>3.6</td>
<td></td>
<td>0.4</td>
<td>0.8</td>
<td>100</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> HB: HPMC-blending; EB: Eudragit RS 30D-blending; CB: Chitosan-blending.
In vitro release study

An in vitro dissolution test of felodipine from alginate microspheres was carried out in triplicate using USP paddle method at a stirring rate of 50 rpm at 37°C in 500 ml of phosphate buffered saline (PBS, pH 7.4) containing tween 80 (0.5% v/v). Dried microspheres (100 mg) were placed into the medium and the paddle was rotated. A sample (1 ml) was taken at a given interval and placed into the tube while 1 ml of fresh PBS solution was replaced. The taken sample was analysed by a UV spectrophotometer at 362 nm (Ultraspec 2000, Pharmacia Biotech, Sweden).

Results and discussion

Average diameter of alginate microspheres

Tables 3 and 4 exhibit the average diameter of polymer-coated and blended alginate microspheres, respectively. As the amount of polymer in the coating solution increased, the average diameter of coated alginate microspheres increased. This may be attributed to the increased amount of polymer on the microsphere surface. As seen in tables 3 and 4, the average diameters of Eudragit RS 30D-coated or blended alginate microspheres (EC, EB formulations) were longer than those of other formulations.

Encapsulation efficiency

The encapsulation efficiency of alginate microspheres prepared in this experiment was generally high, as seen in tables 3 and 4. However, encapsulation efficiency of some formulations among coated microspheres was lower than other formulations. It can be explained that drug was diffused out slightly during coating process. The encapsulation efficiency of plain alginate microspheres was higher than that of Chan et al. (1997) or Gürsoy and Ceviik (2000).

Morphological Analysis

Figure 2 shows the surface morphologies of polymer-coated and blended alginate microspheres. While HPMC or Eudragit RS 30D-coated microsphere had rough surface, chitosan-coated microsphere had smoother surface and smaller

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Average diameter ± SD (µm)</th>
<th>Encapsulation efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>347 ± 61</td>
<td>90.4 ± 1.6</td>
</tr>
<tr>
<td>HC1</td>
<td>350 ± 80</td>
<td>83.9 ± 7.4</td>
</tr>
<tr>
<td>HC2</td>
<td>397 ± 92</td>
<td>88.8 ± 8.7</td>
</tr>
<tr>
<td>HC3</td>
<td>427 ± 82</td>
<td>93.8 ± 4.6</td>
</tr>
<tr>
<td>EC1</td>
<td>440 ± 69</td>
<td>61.1 ± 2.3</td>
</tr>
<tr>
<td>EC2</td>
<td>463 ± 55</td>
<td>79.5 ± 6.7</td>
</tr>
<tr>
<td>EC3</td>
<td>523 ± 0</td>
<td>64.1 ± 4.0</td>
</tr>
<tr>
<td>CC1</td>
<td>330 ± 68</td>
<td>60.9 ± 1.2</td>
</tr>
<tr>
<td>CC2</td>
<td>320 ± 32</td>
<td>58.0 ± 0.9</td>
</tr>
<tr>
<td>CC3</td>
<td>323 ± 46</td>
<td>86.7 ± 8.4</td>
</tr>
</tbody>
</table>
pores than those of plain alginate microspheres. Chitosan-coating provided a smooth and spherical morphology (Hari et al. 1996, Rebeiro et al. 1999). The surface of polymer-blended alginate microsphere was generally not smooth.

**Drug release from HPMC-coated and blended alginate microspheres**

The release profiles of HPMC-coated alginate microspheres are seen in figure 3. The HC1 formulation produced no effect on the drug release. The drug release from HC3 formulation was not retarded until 30 min, but slightly controlled after 40 min. The HC3 formulation released 78% of drug within 60 min, whereas control achieved 94% drug release. As the amount of HPMC increase in the coating solution, the release rate of drug from coated alginate microspheres was slightly reduced due to the increased amount of HPMC on the microsphere surface. HPMC-coated alginate microspheres produced a slight effect on the release rate of drug.

The release profiles of drug were determined for HPMC-blended alginate microspheres, as shown in figure 4. HPMC-blended alginate microspheres, showed an ideal linear release profile. Difference in release characteristics was not specifically determined, varying HPMC amounts. While 94% of drug was released from control, only 35% was released from HB3 formulation during 1 h. HPMC-blended alginate microspheres swelled but withstood the disintegration longer than other alginate microspheres prepared in this experiment.

HPMC was added to sodium alginate as an additive polymer to modify the drug release from the microspheres. It was reported that HPMC polymers affected the drug release of alginate microspheres (Chan et al. 1997) and increasing the HPMC amount in tablets decreased the release rate of drug (Gürsoy and Cevik 2000). In this experiment, blending HPMC with sodium alginate affected the release rate of drug from alginate microspheres as a result of protection from erosion and disintegration. HPMC was found to be an effective additive polymer for controlling the release rates (Gürsoy et al. 1998). This may be attributed to the chemical nature of the HPMC as well as its viscosity (Chan et al. 1997). Microspheres with tight polymer structures could be produced because the long, partially coiled HPMC polymer chains could interpenetrate the sodium alginate polymer network (Chan et al. 1997). Therefore, HPMC-blended alginate microsphere is a good candidate for controlling the drug release.

### Table 4. Average diameter and encapsulation efficiency of polymer-blended alginate microspheres.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Average diameter ± SD (μm)</th>
<th>Encapsulation efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB1</td>
<td>317 ± 65</td>
<td>74.5 ± 5.2</td>
</tr>
<tr>
<td>HB2</td>
<td>320 ± 70</td>
<td>61.7 ± 7.1</td>
</tr>
<tr>
<td>HB3</td>
<td>357 ± 42</td>
<td>72.3 ± 9.3</td>
</tr>
<tr>
<td>EB1</td>
<td>443 ± 46</td>
<td>64.9 ± 5.8</td>
</tr>
<tr>
<td>EB2</td>
<td>457 ± 90</td>
<td>87.2 ± 5.1</td>
</tr>
<tr>
<td>EB3</td>
<td>467 ± 98</td>
<td>73.7 ± 4.7</td>
</tr>
<tr>
<td>CB1</td>
<td>387 ± 48</td>
<td>67.7 ± 4.2</td>
</tr>
<tr>
<td>CB2</td>
<td>390 ± 85</td>
<td>83.5 ± 6.0</td>
</tr>
</tbody>
</table>
Figure 2. SEM micrographs: (a) control, (b) HC3, (c) EC3, (d) CC3, (e) HB3, (f) EB3, (g) CB2.
Figure 3. The release of drug from HPMC-coated alginate microspheres in PBS at pH 7.4 and 37°C ( ■ control, ◆ HC1, ▲ HC2, ○ HC3). Error bars represent ± SD (n = 3).

Figure 4. The release of drug from HPMC-blended alginate microspheres in PBS at pH 7.4 and 37°C ( ■ control, ◆ HB1, ▲ HB2, ○ HB3). Error bars represent ± SD (n = 3).
**Drug release from Eudragit RS 30D-coated and blended alginate microspheres**

Eudragit RS 30D was used as a coating material and an additive polymer. Commercially available Eudragit RS 30D is an aqueous dispersion containing 30% (w/v) copolymer of acrylic and methacrylic acid esters with a low content (5%) of functional quaternary ammonium groups (Gürsoy et al. 1998). Eudragit RS is slightly permeable to water. Plasticizer was added to Eudragit RS 30D to improve film properties.

The release profiles of Eudragit RS 30D-coated alginate microspheres are shown in figure 5. The drug release of EC3 formulation was slow for the initial 20 min and then increased rapidly up to 75% within 1 h. The EC3 formulation had a slight effect for controlling the release while EC1 and EC2 formulations produced no effect after 20 min. In the case of coated alginate microspheres with a low concentration of coating solution, the coating membrane provided weak protection against swelling and erosion resulting in a higher release rate of drug. It was expected that the cationic ammonium groups in Eudragit RS would interact with anionic sodium alginate to limit the drug diffusion, but didn’t produce the desirable results on the drug release in this experiment.

In another way, it was attempted to bind Eudragit RS within the alginate gel matrices in order to affect the drug release. Figure 6 shows the release profiles of HPMC-blended alginate microspheres. While EB1 formulation exhibited a desirable release profile, EB2 and EB3 formulations showed the opposite results on the drug release. The release rates of the drug in the EB2 and EB3 formulations were higher than that in the control for the initial 40 min. This result may be due to the

![Figure 5. The release of drug from Eudragit RS 30D-coated alginate microspheres in PBS at pH 7.4 and 37 °C (control, EC1, EC2, EC3). Error bars represent ± SD (n = 3).](image-url)
decreased density of alginate microspheres, increasing the amount of Eudragit RS 30D (aqueous dispersion) added in alginate solution. This effect accelerates the release rate by decreasing the interaction between Eudragit RS and sodium alginate. When small amounts of Eudragit RS 30D were added to alginate microspheres, Eudragit RS could produce the desirable effect and modify controlled release properties.

Drug release from chitosan-coated and blended alginate microspheres

The release profiles of chitosan-coated alginate microspheres are seen in figure 7. The CC3 formulation released 39% of drug within 1 h, whereas control reached 94% of drug release. The CC3 formulation slowed down the release rate, releasing 65% of drug during 3 h. As the concentration of chitosan-coating solution increases, the drug release was significantly reduced due to increased chitosan interaction on the surface of alginate microspheres.

The alginate microspheres swell and then disintegrate due to the release of the calcium ions by sodium or phosphate (Takka and Acartürk 1999). The swelling and disintegration of alginate microspheres is an important factor in the release of drug. To prevent these factors, alginate microspheres were coated with chitosan, which could strengthen the alginate matrix and reduce membrane permeability. Chitosan-coated alginate microspheres resulted from the electrostatic interaction between carboxyl groups of the alginate with the amine groups of chitosan and reduced the erosion at pH 7–7.5 (Takka and Acartürk 1999). The alginate-chitosan
interaction may be proper to control the release rate and enhance the bioavailability of drug in the intestine (Ribeiro et al. 1999). The slower rate of release from coated microspheres was suited as a delivery vehicle for drug.

Figure 8 exhibits the release profiles of chitosan-blended alginate microspheres. The drug release of CB2 formulation was slower than CB1 formulation. While control reached 94% of drug release, CB2 formulation released 33% of drug during 1 h, showing nearly linear release profiles. As the amount of polymer in sodium alginate or coating solution increase, the drug release from chitosan-blended alginate microspheres was further controlled. However, when the higher amount of chitosan (>10%) was added to alginate solution, it was difficult to produce microspheres because of increased viscosity of polymer mixture. Therefore, an attempt to increase the chitosan to alginate ratio more than CB2 formulation was abandoned. The CB2 formulation exhibited a desirable release profile, but it was non-spherical, irregular. There have been few published studies on chitosan-blended alginate microspheres, contrary to many studies on chitosan-coated alginate microspheres.

**Conclusion**

The plain alginate microsphere showed a fast release of drug as a result of the swelling and disintegration in simulated intestinal media. To prevent a rapid drug release, alginate microspheres were coated or blended with polymers. Chitosan-
coating and HPMC-blending provided an extended release of drug. Moreover, Chitosan-coated microspheres showed a smooth and round surface and HPMC-blended microspheres exhibited a linear release profile. As the amount of polymer in sodium alginate or coating solution increased, the drug release decreased.

In conclusion, HPMC-blended alginate microspheres can easily be made and used for controlled drug delivery systems due to a convenient process and controlled drug release, compared with chitosan-coated microspheres.

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References


