Original Article

Formulation of Sustained Release Metformin Hydrochloride Matrix Tablets: Influence of Hydrophilic Polymers on the Release Rate and In Vitro Evaluation

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Abstract

Metformin HCL, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus acts by decreasing hepatic glucose output and peripheral insulin resistance. It has relatively short plasma half life, low absolute bioavailability. The overall objective of the present work was to develop an oral sustained release metformin tablet prepared by direct compression method, using hydrophilic hydroxyl propyl methylcellulose and Xanthan gum polymer as rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and in vitro drug release. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Hydrophilic matrix of HPMC alone could not control the Metformin release effectively for 12 h whereas when combined with Xanthan gum could slow down the release of drug and can be successfully employed for formulating sustained-release matrix tablets. Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release. Similarity factor, f2 values suggest that the test and reference profile are identical.

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Key words: HPMC K100M, Xanthan gum, Matrix tablets, Release kinetics, Similarity factors

1. Introduction

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance [1,2]. Many innovative methods have been developed for obtaining modified drug release. From the practical view point, hydrophilic matrix tablet is one of the least complicated approaches for developing modified release dosage form.

Hydroxypropylmethylcellulose (HPMC) is hydrophilic cellulose ether widely used as a pH-independent gelling agent in controlled release preparation, due to their release behavior of the drug [3]. Due to non-toxicity, easy handling and no requirement of specified technology for production of sustained release tablets, HPMC is often used as release retarding materials [4]. The transport phenomena
involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly [5]. The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution. The dissolution can be diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer.

Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance. Xanthan gum is a high-molecular-weight extracellular polysaccharide produced by fermentation process of gram negative bacterium Xanthomonas campestris. Xanthan gum is biodegradable and biocompatible and forms gel in water hence, appears to be gaining appreciation for the fabrication of matrices with controlled drug release characteristics [6-9]. The gel forming properties of HPMC and XG can be used to develop sustained release dosage forms. Hydrophilic matrix system release drug sequentially by swelling to form gel, diffusion of drug molecules and finally surface erosion of matrix[7].

Metformin HCl, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus (T2DM), acts by decreasing hepatic glucose output and peripheral insulin resistance [10]. The advantages of metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality [11]. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 h [12, 13].

An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea, that especially occur during the initial weeks of treatment [14]. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release (SR) formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance.

The overall objective of this study was to develop matrix sustained-release tablets of metformin using natural gums (xanthan gum) as suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (hydroxypropyl methylcellulose) with respect to in vitro drug release rate.

2. Materials and methods
2.1. Materials
Metformin hydrochloride was obtained from Vama pharmaceuticals (Nagpur, India). Microcrystalline cellulose (MCC, Avicel pH 101) was purchased from S. D. Fine Chem. Labs, (Mumbai, India). Hydroxypropyl methylcellulose K100M were obtained as a gift sample from colorcon, Mumbai, xanthan gum was obtained as gift samples from Zydus Healthcare Pvt. Ltd. Ahmedabad.. All other ingredients used were of laboratory reagents and used as such without further testing.

Table 1. Composition of Various Trial Formulations for the SR tablet containing metformin HCl

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Ingredients (mg.)</th>
<th>Metformin HCL</th>
<th>HPMC K 100M</th>
<th>Xanthan Gum</th>
<th>MCC</th>
<th>Mg.stearate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td></td>
<td>500</td>
<td>100</td>
<td></td>
<td>390</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>F2</td>
<td></td>
<td>500</td>
<td>150</td>
<td></td>
<td>340</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>F3</td>
<td></td>
<td>500</td>
<td>200</td>
<td></td>
<td>290</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>F4</td>
<td></td>
<td>500</td>
<td></td>
<td>100</td>
<td>390</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>F5</td>
<td></td>
<td>500</td>
<td></td>
<td>200</td>
<td>290</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>F6</td>
<td></td>
<td>500</td>
<td></td>
<td>50</td>
<td>290</td>
<td>10</td>
<td>1000</td>
</tr>
<tr>
<td>F7</td>
<td></td>
<td>500</td>
<td></td>
<td></td>
<td>100</td>
<td>290</td>
<td>1000</td>
</tr>
<tr>
<td>F8</td>
<td></td>
<td>500</td>
<td></td>
<td></td>
<td>50</td>
<td>290</td>
<td>1000</td>
</tr>
</tbody>
</table>

2.2. Methods
2.2.1. Study of physical interaction between drug and polymer.
Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 cm⁻¹ using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan ). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer. DSC study of untreated and spray-dried metformin hydrochloride samples were carried out on a differential scanning calorimeter (model DSC7, Perkin Elmer, UK). Samples, of 2 mg each, of untreated drug and spray-dried powder of the optimized batch were held for 1 minute at 50 °C and then heated gradually at 10 °C min⁻¹ in crimped aluminum pans under a nitrogen atmosphere from 50 to 270 °C. The onsets of melting points and enthalpies of fusion of samples were automatically calculated by the instrmtment.

2.2.2. Preparation of metformin hydrochloride matrix tablets
Different matrix embedded formulations of metformin hydrochloride were prepared by direct compression method using varying proportion of polymers either alone or in
Table 2. Physical properties of the matrix tablets containing 500 mg metformin HCl as a SR formulation

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Hardness† (kg/cm²)</th>
<th>Friability† (%)</th>
<th>Weight Variation* (%)</th>
<th>Drug Content* (%)</th>
<th>Thickness† (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.39±0.36</td>
<td>0.12±0.14</td>
<td>1001.68±2.13</td>
<td>99.54</td>
<td>4.42±0.06</td>
</tr>
<tr>
<td>F2</td>
<td>7.10±0.58</td>
<td>0.28±0.11</td>
<td>1001.28±4.13</td>
<td>99.84</td>
<td>4.53±0.04</td>
</tr>
<tr>
<td>F3</td>
<td>7.55±0.63</td>
<td>0.29±0.12</td>
<td>1001.48±3.13</td>
<td>97.23</td>
<td>4.29±0.07</td>
</tr>
<tr>
<td>F4</td>
<td>6.12±0.12</td>
<td>0.27±0.19</td>
<td>1001.68±6.13</td>
<td>98.24</td>
<td>4.53±0.09</td>
</tr>
<tr>
<td>F5</td>
<td>6.54±0.22</td>
<td>0.38±0.42</td>
<td>1002.38±5.83</td>
<td>99.44</td>
<td>4.59±0.06</td>
</tr>
<tr>
<td>F6</td>
<td>6.82±0.54</td>
<td>0.37±0.61</td>
<td>999.26±3.46</td>
<td>97.84</td>
<td>4.52±0.06</td>
</tr>
<tr>
<td>F7</td>
<td>6.90±0.83</td>
<td>0.54±0.45</td>
<td>999.38±6.43</td>
<td>97.34</td>
<td>4.52±0.05</td>
</tr>
<tr>
<td>F8</td>
<td>6.62±0.28</td>
<td>0.29±0.58</td>
<td>1004.18±3.44</td>
<td>97.44</td>
<td>4.42±0.03</td>
</tr>
</tbody>
</table>

combination. The composition of various formulations of the tablets with their codes is listed in Table 1. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, polymer (HPMC, Xanthan gum) and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a eight station rotary press (Rimek Minipress I Ahmadabad, India) at a constant compression force equipped with a 14-mm flat-faced punches at a compression force required to produce tablets of about 7–8 kg/cm² hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

2.2.3. Evaluation of tablets

The prepared matrix tablets were characterized immediately after preparation for hardness, weight variation, thickness, friability and drug content [15,16]. The weight variation of the tablets was evaluated (n=20) tablets using an electronic balance. The hardness of the tablets (n=6) was tested using a Monsanto hardness tester (Campbell Electronics, India). Friability (n=10) was determined in a Roche friabilator (Campbell Electronics, India) for 4 minutes at a speed of 25 rpm. (Campbell Electronics, India). The thickness of the tablets was measured by vernier caliper. Drug content was analyzed by measuring the absorbance of standard and samples at λ = 233 nm using UV/Visible spectrophotometer (Shimadzu 1601, Kyoto, Japan).

2.2.4. In-vitro drug release studies

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Electrolab, Mumbai, India) at a rotational speed of 50 rpm at 37±0.5 ºC. The dissolution media used were 900 mL of 0.1 mol/L HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for

Figure1.
DSC of pure metformin hydrochloride (a), physical mixtures of metformin hydrochloride with HPMC K100 M (b) and Xanthan gum (c)
12h. Sink condition was maintained for the whole experiment. Samples (10 mL) were withdrawn at regular intervals and the same volume of prewarmed (37±0.5 °C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 μm membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 233 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

2.2.5. Release kinetics
Different kinetic equations (zero-order, first-order, and Higuchi’s equation) were applied to interpret the release rate of the drug from matrix systems [17-19]. The best fit with higher correlation (r² = 0.98) was found with Higuchi’s equation for all the formulations. Two factors, however, diminish the applicability of Higuchi’s equation to matrix systems. This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation [19] which is often used to describe drug release behavior from polymeric systems:

\[ M_t / M_\infty = K.t^n \]

Where,
- \( M_t / M_\infty \) = fraction solute release
- \( t \) = release time
- \( K \) = kinetic constant characteristic of the drug/ polymer system
- \( n \) = exponent that characterizes the mechanism of release of traces

Based on various mathematical models, the magnitude of the release exponent “n” indicates the release mechanism (i.e. Fickian diffusion, case II transport, or anomalous transport). In the present study, the limits considered were \( n = 0.45 \) (indicates a classical Fickian diffusion-controlled drug release) and \( n=0.85 \) (indicates a case II relaxational release transport; non-Fickian, zero-order release). Values of \( n \) between 0.45 and 0.85 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport.

In order to compare the release profile of different formulations with possible difference in release mechanisms (n values), a mean dissolution time (MDT) [20] was calculated using the following equation.

\[ \text{MDT} = (n/n+1). K^{1/n} \]

Where \( n = \) release exponent and \( k = \) release rate constant

To evaluate and compare dissolution data, the dissolution profile was statistically analyzed using dissolution similarity factor \( f_2 \) [19]. The equation for calculating \( f_2 \) is given below.

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

Where, \( n = \) numbers of dissolution time point
- \( W_t = \) Optional weight factor
- \( R_i = \) Reference dissolution point at time \( t \)
- \( T_i = \) Test dissolution point at time \( t \)

The \( f_2 \) value between 50 and 100 suggest that the dissolution is similar. The \( f_2 \) values of 100 suggest that the test and reference profile are identical and as the value becomes smaller, the dissimilarity between release profile increases.

2.2.6. Scanning electron microscopy (SEM)
Electron micrographs metformin hydrochloride matrix tablets before and after dissolution was obtained using a scanning electron microscope (model JSM T200, Joel Ltd., Japan). The specimens were coated under vacuum with gold in an argon atmosphere prior to observation. The scanning electron microscope was operated at an acceleration voltage of 30kV.

2.2.7. Statistical Analysis
The data was subjected to two ways ANOVA followed by Bonferroni post test for analyzing the statistical difference using the software Graph pad prism (San Diego, CA) and in all the cases p < 0.001 was considered as significant.

Figure 2.
FT-IR spectra of pure metformin hydrochloride (a), and Physical mixtures of metformin hydrochloride with HPMC K100 M (b) and Xanthan gum (c).

3. Results
3.1. Study of physical interaction between drug and polymer
FTIR studies revealed that metformin hydrochloride showed two typical bands at 3369 and 3296 cm⁻¹ due to N-H primary stretching vibration and a band at 3170 cm⁻¹ due to N-H secondary stretching, and characteristics bands at 1626 and 1567 cm⁻¹ assigned to C=N stretching. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride with HPMC K100 M (b) and Xanthan gum (c).
3.2. Tablet characteristics
The tablet hardness, thickness, weight variations, and friability for each formulations are presented in Table 2. Friability value of all formulations and commercial tablets were less than 1%. The average percentage deviation of all tablet formulations was found to be within the above limit, as per official pharmacopeia requirements. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 95%.

3.3. Drug release studies
The results of dissolution studies as shown in fig 3 indicate that formulations F1, F2, F3 released 47.9, 29.6 and 23.7% of drug, after 2h and 98.7, 97.4 and 96.6% of drug, respectively, after 10 h. Formulations containing xanthan gum (fig 3) F4, F5 released 54.88, 49.22 % and 98.03, 93.85% of drug, respectively, after 2h and 8h. The dissolution profile of metformin tablets containing combinations of a hydrophilic polymer HPMC with Xanthan gum in the different polymer/polymer ratio (75:25, 50:50 and 25:75 respectively) while keeping the total polymer ratio 20% are shown in figure 4. Formulations F6, F7 and F8 released 47.8, 33.7 and 31.45% of drug, respectively, after 2h and 97.6, 97.5 and 96.8% of drug respectively, after 12. Marketed formulation Glycomet SR showed 28.50% at 2h and 96.52% at 12h.

3.4. Release kinetics
To describe the kinetics of drug release from matrix tablets, release data was analyzed according to different kinetic equations. The data were analyzed by the regression coefficient method and regression coefficient value (r²) of all batches were shown in Table 3. The in vitro release profiles of drug from all these formulations could be best expressed by Higuchi’s equation as the plots showed highest linearity (r²=0.98to 0.99). To confirm the diffusion mechanism, the data were fitted into Korsmeyer- Peppas equation the formulations showed good linearity (r² = 0.98 to 0.99) with slope (n) between 0.437- 0.666. The time taken to release 25% (t25), 50% (t50), and 75% (t75) of drug from different formulations was determined (Table 4). Marketed formulation Glycomet SR when compared with F5 the f2 values found to be 73. The SEM images of the tablet were taken before and after dissolution as shown in Figure 5.

3.5 Statistical Analysis
The data was subjected to two ways ANOVA followed by Bonferroni post test for analyzing the statistical difference using the software Graph pad prism (San Diego, CA)
4. Discussion

4.1. Study of physical interaction between drug and polymer

No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed. The DSC curve of pure metformin exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237 °C (Tonset = 231.2, Tpeak = 233.33 and ΔHfusion = -313.51 J/g). The thermal curves of both binary and ternary mixtures, obtained by simple blending corresponded to the superimposition of those of the single components, indicating the absence of solid-state interactions and allowing assessment of drug–polymers compatibility in all the examined formulations. As a further confirmation of the absence of any incompatibility problem, no variations in the thermal behavior of samples of binary and ternary combinations were observed after their tabletting and subsequent powdering. Thus no definite solid-solid interaction could be concluded Examination of all the DSC thermograms.

4.2. Tablet characteristics

All the tablets of different formulations showed acceptable results with respect to weight variation, drug content uniformity and friability. In determinations of tablet weights, all formulations weights were found to be within pharmacopoeia limits. A plain punch with the same radius each time was used for all formulations in tablet pressing, and the differences in tablet radius was not significant (P < 0.05). Friability of the tablet was well within the acceptable range of 1% and indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed [21]. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the uniformity of weight as per official Pharmacopeia. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets, and drug content was more than 95%.

4.3. Drug release studies

The results as shown in Fig 3 indicate that the release rate decreased as the concentration of HPMC K100M increased. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug [22] and is more likely to be resistant to drug diffusion and erosion [23]. This indicates that drug/polymer ratio is important factors affecting the rate of release drugs from HPMC matrices Factors that may contribute to differences in drug dissolution profile as a function of changes in total polymer concentration include...
differences in water penetration rate, water absorption capacity and polymer swelling [24].

**Table 4: Dissolution Parameter of Sustained Metformin Hcl Matrix Tablets**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>t 25 % (h)</th>
<th>t 50 % (h)</th>
<th>t 75 % (h)</th>
<th>MDT (h)</th>
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<tbody>
<tr>
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<td>0.5</td>
<td>2.2</td>
<td>4.8</td>
<td>2.11</td>
</tr>
<tr>
<td>F2</td>
<td>0.6</td>
<td>2.5</td>
<td>5.6</td>
<td>3.14</td>
</tr>
<tr>
<td>F3</td>
<td>1.2</td>
<td>3.5</td>
<td>6.7</td>
<td>3.91</td>
</tr>
<tr>
<td>F4</td>
<td>0.3</td>
<td>1.7</td>
<td>4.1</td>
<td>2.42</td>
</tr>
<tr>
<td>F5</td>
<td>0.5</td>
<td>2.2</td>
<td>4.9</td>
<td>2.64</td>
</tr>
<tr>
<td>F6</td>
<td>0.5</td>
<td>2.3</td>
<td>5.9</td>
<td>3.30</td>
</tr>
<tr>
<td>F7</td>
<td>1.2</td>
<td>3.8</td>
<td>7.4</td>
<td>4.27</td>
</tr>
<tr>
<td>F8</td>
<td>1.3</td>
<td>4.4</td>
<td>8.8</td>
<td>4.98</td>
</tr>
<tr>
<td>GLUCOMET SR</td>
<td>1.3</td>
<td>4.1</td>
<td>8.1</td>
<td>4.69</td>
</tr>
</tbody>
</table>

Formulations formed with xanthan gum showed initial burst release (fig 4) and slow drug release with increasing concentration of polymer which may be due to formation of a thick gel layer with increasing viscosity around the tablets by quick hydration of XG matrices. In the formulation containing combination of polymers, When HPMC K100M is replaced by the Xanthan Gum, decrease in the drug release were observed (fig 5) which clearly indicates that Increasing the concentration of xanthan gum in the matrix alters the drug release profile significantly.

### 4.4. Drug release kinetics

On analyzing regression coefficient values of all batches, it was found that formulation F1,F2, and F5 exhibit Higuchi release kinetics whereas, Batch F3,F4,F6,F7 and F8 followed Korsmeyr –peppas model. The data fitted into Korsmeyer-Peppas equation appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion. Mean dissolution time (MDT) value is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. Comparing the MDT of tablets with double combination of polymers with a 2-way ANOVA test showed that the type of the combination of 2 polymers, the ratio of the 2 polymers and also their interaction effects had main effect on MDT (P <0.05). This test shows that the combination of a xanthan gum with HPMC leads to a greater MDT compared with the individual polymers,which clearly indicated sustained release nature of the combination.

The time taken to release 25% (t25), 50% (t50), and 75% (t75) of drug from different formulations clearly indicates the sustained behavior of the combination of polymers. 

SEM before dissolution (Fig.5 a) showed intact surface without any perforations, channels, or troughs. After dissolution, (Fig.5 b) revealed many pores with increasing diameter. The solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium, which clearly indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of metformin from formulated matrix tablets.

### 4.5. Statistical Analysis

The data was subjected to two ways ANOVA followed by Bonferroni post test and in all the cases p < 0.001 was considered as significant.

### 5. Conclusions

The findings of the present study demonstrate that the hydrophilic matrix of HPMC alone could not control the Metformin HCL release effectively for 12 h whereas when combined with xanthan gum could slow down the release of drug from their matrices and can be successfully employed for formulating sustained-release matrix tablets. Diffusion coupled with erosion might be the mechanism for the drug release which can be expected to reduce the frequency of administration and decrease the dose-dependent side effects associated with repeated administration of conventional metformin HCL tablets.

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References


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