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Abstract: A Quaternary Mg-Zn-Ca-based alloy and a heat treatment process for producing biodegradable bone fixation implants are described thereof. The mechanical and biocorrosion properties of the fabricated Mg-based alloy were improved by combining careful selection of the alloy's chemical composition and subsequent post-shaping process (heat treatments). Heat treatment process is more privileged especially after fabricating the part into its final shape such as in additive manufacturing (3D-printing) and powder metallurgy. In this way, it is possible to produce biocompatible, strong and less corrosive patient-specific bone fixation hardware. Also, such heat-treated Mg-Zn-Ca-based parts can be further coated with various types of biocompatible ceramic coatings for slower and more tailored biocorrosion rates.

[Continued on next page]

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PROCESS TO PRODUCE HIGH-STRENGTH AND CORROSION RESISTANT ALLOY FOR PATIENT-SPECIFIC BIORESORBABLE BONE FIXATION IMPLANTS AND HARDWARE

CROSS REFERENCE TO RELATED APPLICATION
The present patent application is based upon and claims the benefit of provisional patent application No. 62/270,227 filed December 21, 2016.

BACKGROUND OF THE INVENTION
This invention relates to a biocompatible Mg-Zn-Ca-based alloy and a post-shaping heat treatment process for the production of patient-specific bioresorbable bone fixation hardware.

Mg-Zn-Ca-based alloys are the most promising alloy system for bone implant applications mainly due to their superior biocompatibility. For patient-specific (3D-printed) fixation hardware made of an Mg-Zn-Ca-based alloy, heat treatment can be used to improve the mechanical properties of such alloys by means of intermetallic precipitations.

Some efforts have been made to improve the mechanical and/or corrosion properties of metallic alloys using different heat or mechanical treatment processes. As an example, Kaese et al., as described in US Pat. No. 6,854,172, B2, used casting process, heat treatment, particularly homogenization, a subsequent thermomechanical treatment, particularly extrusion and finally cutting process to produce a pin-shaped thin-walled tubular implant for cardiovascular supports made of Mg or Zn alloys.

For Mg-Zn-Ca based alloys, different heat treatment methods have been done to enhance their mechanical or corrosion properties such as annealing, solution treatment, quenching and age hardening. Most of them were mainly performed to enhance the mechanical properties of such alloys mainly for structural applications without investigating the effect of heat treatment on the biocompatibility and biocorrosion properties of these alloys. For example, the method followed in the work of Oh-Ishi et al. entitled "Age-Hardening Response of Mg-0.3 at %Ca Alloys with Different Zn Contents'
was focused only on enhancing the hardness as a measure of mechanical properties of the Mg-0.5wt%Ca alloys with 0 to 4.2 wt.%Zn.

Only two efforts paid attention to the effect of heat treatment on the biocorrosion behavior of Mg-Zn-Ca-based alloys as a potential bone fixation application. The first effort is the work of Lu et al. entitled "Effects of Secondary Phase and Grain Size on the Corrosion of Biodegradable Mg-Zn-Ca Alloys". In this work, only solution treatment and quenching were performed on Mg-3wt.%Zn-0.3wL%Ca alloy without performing any age hardening process. They found an enhancement in the alloy's biocorrosion resistance after solution treatment and quenching. However, the resulting alloy's mechanical properties after heat treatment were not investigated.

The second effort is the work of Ji et al. entitled "Influence of Heat Treatment on Biocorrosion and Hemocompatibility of Biodegradable Mg-35Zn-3Ca Alloy". An enhancement in the biocorrosion resistance and biocompatibility of the heat-treated alloy was found. However, the effect of the heat treatment process on the mechanical properties for the studied alloy (Mg-35wt.%Zn-3wt.%Ca) was again ignored, similar to the previously mentioned efforts. In addition, the studied alloy in the Ji et al. work has significantly high content of alloying elements especially Zn (35 wt.%). It has been reported in several studies that high loading of Zn causes an excess formation of \( \text{Ca}_2\text{Mg}_6\text{Zn}_3 \) secondary phase which suppresses the formation of the finely dispersed monolayer Guinier-Preston (G.P.) zones leading to lower age hardening effect, hence less mechanical properties enhancement.

In general, using heat treatment for developing Mg-Zn-Ca-based bone fixations should consider the following aspects: (i) proper choice of the alloy chemical composition, (ii) proper choice of the heat treatment processes and parameters, (iii) assessment of mechanical properties and (iv) assessment of biocorrosion properties after heat treatment. None of the previous heat treatment methods covered all these needed aspects.
SUMMARY OF THE INVENTION

Accordingly, an object of subject invention is to carefully cover these aspects to provide a process for producing a Mg-Zn-Ca-based alloy for bone fixation hardware.

Another object is the development of a novel Mg-Zn-Ca-based alloy and a heat treatment method that, in addition to its role in improving the Mg-Zn-Ca-based alloy's mechanical properties, also significantly enhances its biocorrosion properties.

This enhancement in the biocorrosion properties is represented in a significantly slower degradation rate and a more uniform (predicted) degradation of the heat-treated Mg-Zn-Ca alloy compared to the as-cast one in a simulated body fluid medium (in-vitro tests). The slower in-vitro degradation rate and higher strength of the heat-treated alloy indicates that this heat treatment method is a promising post-shaping process for the prepared Mg-Zn-Ca-based alloy in order to produce biocompatible, strong and less biocorrosive devices for bone fixation and applications.

Still another subject improvement and preferred embodiments of the invention are described in detail hereinafter.

Other objects and advantages of the present invention will become apparent to those skilled in the art upon a review of the following detailed description of the preferred embodiments and the accompanying drawings.

BRIEF DESCRIPTIONS OF THE DRAWINGS

Figs. 1a through 1f are SEM micrographs of the as-cast compared against the heat-treated alloy.

Figs. 2a and 2b are optical micrographs of the as-cast Mg-Zn-Ca alloy without Mn compared against the as-cast Mg-Zn-Ca alloy with Mn.

Fig. 3a and 3b are SEM micrographs at different magnifications of the ceramic coating created on the heat-treated alloy using MAO.

Fig. 4 is a graph showing mechanical properties.
Fig. 5 is a graph showing polarization curves of as cast versus the heat-treated alloy.

Fig. 6 are photographs of the corroded alloy after in vitro immersion.

Fig. 7 is a graph of in vitro corrosion properties of the alloy of as cast versus the heat-treated alloy.

Fig. 8 is a graph showing mechanical properties.

Fig. 9 is a graph showing polarization curves of the heat-treated alloy.

Fig. 10 is a graph showing mechanical properties of as cast versus the heat-treated alloy with the addition of Mn.

Fig. 11 is a graph showing polarization curves of the heat-treated alloys with the addition of Mn.

Fig. 12 is a graph showing polarization curves of the heat-treated alloy and the MAO coated alloy.

Fig. 13 is a graph of in vitro corrosion properties of the different alloys.

Fig. 14 is a graph of an XRD analysis of the alloy before and after immersion.

**DETAILED DESCRIPTION OF THE INVENTION**

This invention proposes a process in which a Mg-Zn-Ca-based alloy is cast and then heat-treated, particularly solution-treated, quenched and age-hardened. In the preferred embodiment, the Mg-Zn-Ca-based alloy contains Mg-1.2wt%Zn-0.5wt.%Ca. The Mg-Zn-Ca-based alloy was prepared by using commercial Mg, pure Zn, and a 15% Ca-Mg master alloy.

The enhancement in the mechanical properties of Mg-Zn-Ca-based alloys after heat treatment is due to the refinement and uniform distribution of the (α-Mg+Ca2MgZn) eutectic phase into fine dispersions precipitates. Therefore, the chemical composition of the cast Mg-Zn-Ca alloy must be carefully chosen to obtain the optimum age hardening effect after the heat treatment process. For instance, a Ca content of 0.5wt% (less than 1 wt.%, the solubility limit of Ca in Mg) will avoid excess formation of Mg2Ca phase that hinders the age hardening process. Further, any increase in the Ca
content above the solubility limit does not result in more grain refinement. A Zn content of 1.2 wt.% will avoid excess formation of Ca₂Mg₆Zn₃ phase since a high concentration of Ca₂Mg₆Zn₃ phase suppresses the formation of the finely dispersed monolayer Guinier-Preston (G.P.) zones on basal planes leading to a less age hardening effect. Further, a relatively low (below 5 wt.%) Zn content is preferred to avoid formation of the MgZn phase that has no role in the age hardening effect.

This means that the designed Zn/Ca atomic ratios of the prepared alloy (1.47) is within the range of (1.2 to 2.0) for the optimum corrosion properties and age hardening effect. The alloys chemical composition and the level of impurities were evaluated via two different techniques: X-ray florescence (XRF) and energy dispersive spectroscopy (EDS) and they were found to be similar to the designed values.

Heat treatment processes and parameters were chosen carefully to obtain the optimum results. For instance, the as-cast alloy was solution-treated above solidus line at 510 °C for 3 h in an inert gas environment using a tube furnace to assure the melting of MgCa and Ca₂Mg₆Zn₃ eutectic phases in the primary α-Mg matrix. The solution-treated alloy was then quenched in cold water to trap fine dispersions of the Ca₂Mg₆Zn₃ intermetallic phase in the primary α-Mg matrix. Afterwards, the quenched alloy was artificially age-hardened in an oil bath at 200 °C to uniformly distribute the thermally stable (α-Mg+Ca₂Mg₆Zn₃) and/or (α-Mg+Mg₂Ca+Ca₂Mg₆Zn₃) intermetallic phase fine dispersions. The alloy was aged for different durations (1, 2, 3, 5 and 10 hours) to determine which duration produced the optimum age hardening effect on the mechanical and corrosion behavior for bone fixation applications. Similarly, the alloy was aged at different age hardening temperatures (100, 150, 200 and 250 °C) to determine the aging temperature that results in the highest mechanical and corrosion resistance.

The effect of adding 0.5 wt.% Mn on the mechanical and corrosion properties of the ternary Mg-1.2 wt.%Zn-0.5 wt.%Ca alloy was investigated, as well. Finally, the heat-treated Mg-Zn-Ca-based alloy at the optimum
conditions was coated with a biocompatible ceramic coating using a micro arc oxidation (MAO) process for slower and more tailored biocorrosion rates.

The as-cast and heat-treated ingots were cut into the needed sample sizes and carefully prepared for their mechanical and corrosion properties characterization.

Figures 1.a., 1.c and 1.e, show the scanning electron microscope (SEM) micrographs of the as-cast alloy. The formation of the (α-Mg+Ca₂Mg₆Zn₄) secondary phase can be observed as lamellar eutectoids within grain boundaries of the primary α-Mg matrix phase and spherical precipitates within the α-Mg matrix interdendritic interstices. This observation was supported by results from the EDS analysis, as seen in Figure 1.g. The solid solution (point 1) was found to be Mg-rich solution with low content of Zn and Ca which indicates that it is the primary α-Mg phase. The secondary phase (point 2) has a significant higher content of Zn and Ca which indicates that it is the eutectic (α-Mg+Ca₂Mg₆Zn₄) phase.

Figures 1.b., 1.d and 1.f. show the SEM micrographs of the heat-treated alloy. It can be seen that the grains have a dendritic structure with relatively larger grain size compared to the as-cast alloy. Also, the (α-Mg+Ca₂Mg₆Zn₄) secondary phase was refined and converted into uniformly distributed and finely dispersed precipitates within the microstructure after heat-treatment. The results obtained from the EDS analysis for the heat-treated microstructure, Figure 1.h., show similar Mg, Zn and Ca contents at different investigated points within the microstructure which confirms the uniform distribution of Ca₂Mg₆Zn₄ into finely dispersed precipitates. It is well-known that the refinement of secondary phases and the formation of the finely dispersed monolayer Guinier-Preston (G.P.) zones on basal planes are responsible for the age hardening effect after heat treatment.

Figures 2.a. and 2.b. show the optical micrographs of the as-cast Mg-1.2wt%Zn-0.5wt.%Ca alloy in comparison to the Mg-1.2wt%Zn-0.5wt.%Ca-0.5wt.%Mn alloy, respectively. The grain size of the alloy after the addition of Mn was much lower than that for the Mn-free alloy. The average grain size of the Mg-1.2wt%Zn-0.5wt.%Ca alloy and the Mg-1.2wt%Zn-0.5wt.%Ca-
0.5wt.%Mn alloy was around 216 µm and 67 µm, respectively. Such grain refinement effect is expected to result in an improved mechanical and corrosion properties for the Mg alloy before and after heat treatment.

Figure 3 shows the SEM micrographs of a ceramic coating prepared on the heat-treated Mg-Zn-Ca-based alloy using a MAO process.

Figure 4 shows the mechanical properties (micro-hardness and compression) of the as-cast and heat-treated alloy aged at 200 °C. The heat treatment process was found to significantly increase the alloy mechanical properties. Age hardening duration of 2-5 hours showed the optimum mechanical properties. For instance, the tensile and compressive yield strengths of the alloy age-hardened for 3 hours were 1.4 and 1.9 times those for the as-cast alloy, respectively.

The polarization curves for the as-cast and heat-treated alloy tested in m-SBF solution at pH 7.4 and 37 °C are shown in Figure 5. The heat-treated alloy has less negative potential and lower corrosion density than the heat-treated alloy. This indicates that the heat-treated alloy has better electrochemical corrosion characteristics that results in a lower corrosion rate (P) for the heat-treated alloy than the as-cast alloy, as seen in table 1. The best corrosion resistance was obtained for alloy samples aged for 2-5 hours.

Figure 6 shows optical images of degraded as-cast and heat-treated alloy after in vitro immersion in m-SBF at 37 °C and 7.3-7.8 pH for 3, 7, 14, 21 and 28 days. Both as-cast and heat-treated alloy samples showed a small amount of degradation (less than 2 mg/cm²) after immersion for 3 days. However, with increasing the immersion duration (more than 7 days), the degradation of the as-cast alloy increased remarkably compared to the heat-treated alloy samples. On contrary to the heat-treated alloy samples, the as-cast samples showed uneven surface with large cracked regions (pitting corrosion) that were subjected to intense corrosion attack. This is suggested to be due to the presence of larger regions of the (α-Mg+Ca₂Mg₆Zn₃) secondary phase that promotes the galvanic corrosion for the as-cast alloy than the heat-treated alloy. By day 28 of the in vivo immersion test, the as-cast alloy samples were degraded completely, while more than 50 % of the
heat-treated alloy samples (2-10 age hardening durations) remained, see table 2. The age-hardened alloy samples for more than 2 hours have the superior corrosion resistance, see Figure 6, 7. For example, the corrosion rate of the heat-treated alloy aged for 2 to 5 hours was almost half that for the as-cast alloy.

The enhancement in the corrosion resistance of the Mg-Zn-Ca alloy after heat treatment can be attributed to the refinement and fine dispersion of the Ca$_2$Mg$_6$Zn$_3$ phase in the heat-treated alloy. Large precipitates of Ca$_2$Mg$_6$Zn$_3$ phase in the microstructure, as in the case of as-cast alloy, work as cathodic site for the α-Mg matrix phase, hence faster corrosion rate for the as-cast alloy is expected.

Figure 8 shows the effect of aging temperatures on the age hardening response (microhardness) of the heat-treated Mg-1.2wt%Zn-0.5wt.%Ca alloy aged for 3 hours and different aging temperatures. It can be seen that aging the Mg-Zn-Ca-based alloy at 200 °C results in the best age hardening response. Similarly, the effect of aging temperatures on the electrochemical corrosion properties at pH 7.4 and 37 °C of the heat-treated Mg-1.2wt%Zn-0.5wt.%Ca alloy is shown in Figure 9, while table 3 summarizes the electrochemical corrosion characteristics. It is obvious that aging the Mg-1.2wt%Zn-0.5wt.%Ca alloy at 200 °C results in the best corrosion behavior represented in the lowest corrosion rate.

Figure 10 shows the effect of adding Mn on the compression stress-strain diagram of the as-cast and heat-treated Mg-Zn-Ca-based alloys. It can be seen that the age hardening response of the Mg-1.2wt.%Zn-0.5wt.%Ca-0.5wt.%Mn alloy was higher than that for the Mg-1.2wt.%Zn-0.5wt.%Ca alloy. The in vitro electrochemical corrosion test results at pH 7.4 and 37 °C showed significantly lower corrosion rates for the heat-treated Mg-Zn-Ca-based alloy after the addition of 0.5 wt.% Mn, as seen in Figure 11.

The electrochemical corrosion curves of the MAO-coated alloy at pH 7.4 and 37 °C after performing the heat-treatment process at the optimized parameters are shown in Figure 12. It can be seen that the corrosion rate of
the heat-treated Mg-Zn-Ca-based alloy was significantly reduced from 8.7 mm/year to be 0.03 mm/year after the coating process.

The morphologies and the elemental compositions of the as-cast and heat-treated alloy sample degraded surfaces after 3 and 28 days of immersion at 37 °C and 7.3-7.8 pH were studied using SEM investigation and the EDS analysis as shown in Figure 13. All samples showed uneven surface morphology by the 3 day of immersion with corrosion product agglomerations on the surface. The EDS elemental analysis of the agglomerated substance and the ground of the as-cast alloy surface showed large amounts of oxygen, calcium and phosphorus. The heat-treated alloy sample surface showed similar trend for the agglomerated substance. However, no traces of phosphorus on the ground of the corroded surface.

Figure 14 shows the XRD analysis for the heat-treated alloy samples (a) before immersion and (b) after immersion in m-SBF solution at 37 °C and 7.3-7.8 pH for 3 days. The XRD pattern of alloy before immersion showed the presence of small reflections of Mg₂Ca phase, which do not support its presence, and relatively higher intensity of Ca₂Mg₆Zn₃ phase in addition to Mg reflections. These results are in consistent with the microstructural investigation results. The XRD patterns for the alloy after immersion showed the presence of hydroxyapatite (HA) and magnesium hydroxide (Mg(OH)₂) as the main corrosion compounds formed on the surface of the corroded samples. Such biocompatible corrosion products, in addition to its role in bone growth stimulation, it may also act as a corrosion barrier that decelerate corrosion.

It is, therefore, to be understood that the invention may be practiced within the scope of the subjoined claims.

Table. 1 Electrochemical corrosion characteristics of the as-cast and heat-treated alloy with different age hardening durations tested in m-SBF at 37 °C and 7.4 pH.
The above detailed description of the present invention is given for explanatory purposes. It will be apparent to those skilled in the art that numerous changes and modifications can be made without departing from the scope of the invention. Accordingly, the whole of the foregoing description is to be construed in an illustrative and not a limitative sense, the scope of the invention being defined solely by the appended claims.
CLAIMS

We claim:

1. A patient-specific bioresorbable magnesium (Mg) based bone fixation hardware made of a cast alloy consisting of:

   0.75 to 2.0 percent by weight of zinc (Zn);
   0.25 to 1.0 percent by weight of calcium (Ca);
   0.25 to 1.0 percent by weight of manganese (Mn);
   remainder being magnesium (Mg), and

   wherein the cast allow is heat-treated.

2. The magnesium (Mg) based bone fixation hardware according to claim 1 wherein the cast alloy contains:

   1.2 percent by weight of zinc (Zn);
   0.5 percent by weight of calcium (Ca);
   0.5 percent by weight of manganese (Mn); and
   remainder being magnesium (Mg).

3. The magnesium (Mg) based bone fixation hardware according to claim 1 having improved mechanical and biocorrosion properties.

4. The magnesium (Mg) based bone fixation hardware according to claim 1 wherein the corrosion rate of the heat-treated alloy is at-least 40% lower than that of the untreated as-cast alloy.

5. The magnesium (Mg) based bone fixation hardware according to claim 1 having biocompatible corrosion byproducts of hydroxyapatite (HA) and magnesium hydroxide (Mg(OH)2).

6. A process for producing patient-specific bioresorbable magnesium (Mg) based bone fixation hardware comprising the steps of:
producing patient-specific fixation hardware made of an alloy of:

- 0.75 to 2.0 percent by weight of zinc (Zn);
- 0.25 to 1.0 percent by weight of calcium (Ca);
- 0.25 to 0.75 percent by weight of manganese (Mn);
- remainder being magnesium (Mg); and
- heat treating the alloy.

7. The process according to claim 6 wherein the alloy is produced by casting.

8. The process according to claim 7 wherein the cast alloy is atomized into powder and patient-specific fixation hardware is produced by 3D-printing.

9. The process according to claim 6 wherein the heat-treating step is solution treating, quenching and age hardening.

10. The process according to claim 6, wherein the heat-treated alloy possesses improved mechanical and biocorrosion properties.

11. The process according to claim 9 wherein the age hardening is earned out for 2 to 5 hours at 200 °C and the heat-treated alloy possesses half the corrosion rate of the as-cast alloy.

12. The process according to claim 6 wherein the alloy has biocompatible corrosion byproducts of hydroxyapatite (HA) and magnesium hydroxide (Mg(OH)_2).

13. The process according to claim 10 wherein the heat-treated alloy with optimum mechanical and biocorrosion properties is further coated with a ceramic coating using microarc oxidation process.
14. A patient-specific bioresorbable magnesium (Mg) based bone fixation hardware made of a cast alloy comprising:

- 0.75 to 2.0 percent by weight of zinc (Zn);
- 0.25 to 1.0 percent by weight of calcium (Ca);
- 0.25 to 1.0 percent by weight of manganese (Mn);
- remainder being magnesium (Mg);

heat treating the cast alloy; and

wherein the heat treating step utilizes solution treating, quenching and age hardening for 2 to 5 hours at 200 °C.

15. The magnesium (Mg) based bone fixation hardware of claim 14 where in the Zn/Ca atomic ratios of the prepared alloy is within the range of 1.2 to 2.0.

16. The process according to claim 1 wherein the heat-treating step is solution treating, quenching and age hardening.

17. The magnesium (Mg) based bone fixation hardware according to claim 1 wherein the corrosion rate of the heat-treated alloy is at-least 50% lower than that of the untreated as-cast alloy.

18. The magnesium (Mg) based bone fixation hardware according to claim 1 wherein the corrosion rate of the heat-treated alloy is 40% to 60% lower than that of the untreated as-cast alloy.
Fig. 1
Fig. 2
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Fig. 6

SUBSTITUTE SHEET (RULE 26)
Fig. 7
Fig. 8
Fig. 9
Fig. 10
Fig. 11
Fig. 12
Fig. 13

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Energy (keV)
Fig. 14
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8): A61 F 2/86, A61L 31/14, A61L 31/02 (2017.01)

CPC: A61 L 31/48, A61L 31/22, A61F 2/86

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8)-: A61F 2/86, A61L 31/14, A61L 31/02 (2017.01)

CPC: A61L 31/48, A61L 31/22, A61F 2/86

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search symbols used)

PatBase, Google Patents, Google Scholar (without Patents)

Keywords: heat treatment high strength corrosion resistance mg-ca-zn-mn alloy bioreabsorbable bone fixation hardware

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>W O 2014/145672 A 1 (Thixomat, Inc) 18 September 2014 (18.09.2014) Abstract, para [0047], para [0065], para [0013], para [0008], para [0073], para [0074], para [0010], para [0042], para [0062], and entire document</td>
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Further documents are listed in the continuation of Box C.

* Special categories of cited documents:
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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
T document member of the same patent family

Date of the actual completion of the international search
15 February 2017

Date of mailing of the international search report
16 MAR 2017

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