國立臺灣大學 研究成果專利申請表

本校案號：064-160201
(由產學合作總中心填)

105年 2月 18日
受文000545號

請勾選以下兩種選項中的一種（請參考第 2-3 頁的詳細說明）： 2015.05.06 版

■「先期專利申請案」 (即美國 Provisional Application，技術已公開者請勿申請)；

□「後期專利申請案」；針對本發明，是否已向校方提出「先期專利申請案」？□是□否

計畫合作機構	科技部, 長庚紀念醫院 (請填寫本申請案所屬之經費來源，如：科技部、經濟部、農委會等)	□利用本校資源 (勾選本項則無需填計畫名稱及編號)
計畫名稱及編號	硫酸鈣/生物玻璃生物複合材料之開發研究(MOST 103-2221-E-002-077); 發展新型硫酸鈣/生物玻璃陶瓷複合材料作為人工骨之研究(1/2) (CMRPG3E0681) (請填寫衍生本申請案之所有計畫，並附核定清單或契約書影本；填寫空間請自行調整)	
計畫合作期限及金額	(MOST)自 2014 年 08 月 01 日 至 2016 年 07 月 31 日; 共新台幣 3,013,000 元整 (長庚紀念醫院) 104 年 01 月 01 日至 104 年 12 月 31 日; 共新台幣 1,134,983 元整	
發明名稱	Bone void filler	
擬申請之國家	□中華民國 ■美國 □其他：_____	

※附件 (請依「先期專利申請案」或「後期專利申請案」，準備所需文件；標示＊者為必須提供)
※請於『研究成果專利申請表』的 word 檔填寫完成後，務必 email 給所屬之本中心窗口。
(關於本中心各人員執掌暨聯絡資訊，請參連結 http://ord.ntu.edu.tw/CIAC/Responsibilities.aspx)

「先期專利申請案」	■＊技術推廣表(附件一)；■＊技術分類表(附件二) ■＊國立臺灣大學研究成果基本資料表(附件三) ■＊送至美國 USPTO 之技術文件 (可直接用論文，但盡量完整地揭露欲保護範圍技術內容，建議以英文撰寫，可包括圖式；無頁數或格式限制)
「後期專利申請案」	□＊技術推廣表(附件一)；□＊技術分類表(附件二) □＊國立臺灣大學研究成果基本資料表(附件三) □＊費用分攤協議書(附件四)；□＊研究成果專利構想揭露書(附件五) □相關文獻陳報表(附件六) □計畫經費核定清單(科技部計畫)或研究計畫補助合約書影本(非科技部計畫) □已公開或預計公開之相關文件(若於附件三第四點勾選公開或預計公開者) □學位論文口試保密同意書影本 □與本案相關之文獻資料影本

提 案 人：[signature] (簽章)　　單　位：材料系

提案日期：105 年 2 月 18 日　　職　稱：教授

國立臺灣大學產學合作總中心 105. 2. 22 收文

敬 陳
系 主 任　工學院材料科學與工程學系系主任 林招松

院　長　工學院副院長 莊東漢
工學院 顏家鈺(甲) 院長 章

研發處（產學合作總中心）
研 發 長

附件一、技術推廣表(含以下兩頁之中、英文表單)

為協助技術移轉，是否有意願與本中心合作推廣本技術※?

■是(本中心將於技術交易網或各媒合會上發佈此資料)；

□否(原因_____；若有意願使用本技術衍生新創公司者，可勾否)。

※依專利法第七條規定，提案人之各專利案的專利申請權及專利權，皆屬本校所有。

附件一、技術推廣表(含以下兩頁之中、英文表單)

1. 為協助技術移轉，是否有意願與本中心合作推廣本技術※?

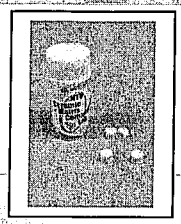
   ■是(本中心將於技術交易網或各媒合會上發佈此資料)；

   □否(若有意願使用本技術衍生新創公司可勾否)。

2. 【勾選『是』者，請於此技術推廣表填寫後，將其 Word 檔及 PDF 檔(5 MB 以下) e-mail 至 ntuciac@ntu.edu.tw，本中心將盡力進行技轉。郵件主旨: 提案老師大名，系所，發明名稱】請中、英文內文皆提供(填寫空間請自行調整)。技術推廣表之表格下載: http://ord.ntu.edu.tw/CO1/download.aspx

※依專利法第七條規定，提案人之各專利案的專利申請權及專利權，皆屬本校所有。

可分解吸收生物陶瓷材料



發明人： 段維新 教授
單　位： 國立臺灣大學　材料學系/研究所
簡　歷： 請點選此連結

市場及需求：

本發明揭露一種可分解吸收生物陶瓷材料，此生物陶瓷不僅可以在生理環境下進行分解及吸收，且分解速率可以調控，可針對不同缺損位置，提供不同的骨修復速率。

技術摘要(含成果)：

本技術揭露的可吸收分解吸收生物陶瓷材料，已經以 5 件專利組合保護，且專利皆已獲證。

優勢：

此創新生物陶瓷具較高強度，生物實驗後，顯示此分解吸收生物陶瓷材料不具毒性，細胞可穩定貼附，可誘發鈣磷酸鹽在表面生成，具生物相容性等諸多優點。

競爭產品：

相較目前市面上骨填充產品，此創新生物陶瓷的強度較高，不具毒性，細胞可貼附，具生物活性。

專利現況：

已領證-- 美國(共 3 件)、中華民國(共 2 件)

- 美國
  - US 8,052,787 B2
  - US 8,263,513 B2
  - US 8,906,817 B2
- 我國
  - I 380832
  - I 488828

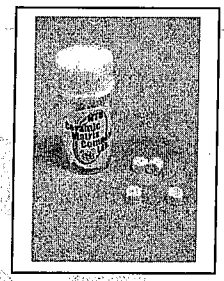
聯絡方式(請不用填)： 臺大產學合作總中心
Tel: 02-3366-9952,　E-mail:laniechen@ntu.edu.tw

Innovative Resorbable Bioceramic

(Below is limited to 1-page only; be careful not to disclose vital technology content. Please delete these words when the document is finished)

PI： Prof. Wei-Hsing Tuan

Department of Materials Science & Engineering, National Taiwan University



Experience:

Market Needs:

An innovative resorbable bioceramic is developed. Comparing to the current products used in hospitals, the bioceramic developed by our team is resorbable within human body fluid. During resorption, our bioceramic can release adequate calcium ions. These ions are helpful to the ingrowth of the bone. The degradation rate of our bioceramic can be tailored through the use of microstructure engineering. The strength of our bioceramic is relatively higher. The cytotoxicity test reveals no toxicity. Cells can attach to the surface of our product.

Our Technology:

The bioceramic developed by our team is resorbable within human body fluid. The patent portfolio combines 5 patents. These patents have been granted already.

Strength:

The strength of our bioceramic is relatively higher. The cytotoxicity test reveals no toxicity. Cells can attach to the surface of our product. Calcium phosphate can be found on the surface of the bioceramic after resorption in body fluid.

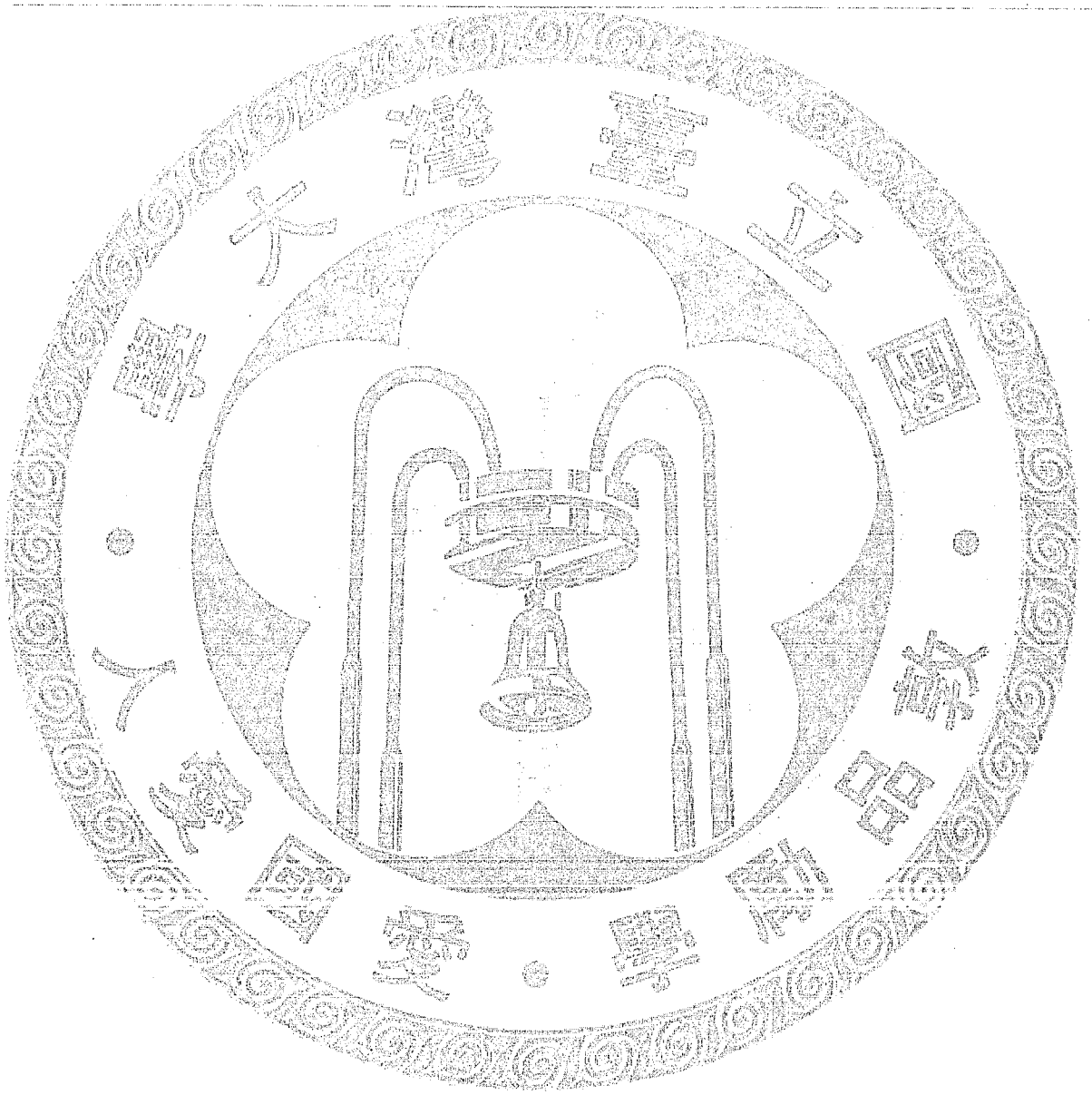
Competing Products:

Comparing to the current bone filler used in hospitals, the bioceramic developed by our team exhibits excellent bio-active characteristics.

Intellectual Properties:

- Granted patents in USA
  - US 8,052,787 B2
  - US 8,263,513 B2
  - US 8,906,817 B2
- Granted patents in Taiwan
  - I 380832
  - I 488828

Contact (do not need to fill out):
Center for Industry-Academia Cooperation, NTU
Tel: 02-3366-9952,　E-mail:laniechen@ntu.edu.tw



附件二、技術分類表

(請依技術本質勾選(可複選)或於其他(請自填)欄位填入適當類別；分類結果將置於網頁)

一階	二階	三階
生醫農健	農業	□植物種苗□動物種苗□生物農藥□生物肥料□生物整治□生物機電□遺傳育種□組織培養□抗病/蟲/逆境性□觀賞□發酵□基因轉殖□糧食□蔬菜□品種權□天然物利用□森林學□獸醫學□其他(請自填)_____
	醫療器材	□診斷與監測用器材□疼痛管理器材□手術與治療用器材□輔助與彌補用器材其他類醫療器材□體外診斷用器材□低/非侵入性器材□預防疾病與健康促進之設備及用品□其他(請自填)_骨替代材_____
	篩選平台	□抗體□生物晶片□細胞分析□組合式分子生物□組合化學□蛋白酶□藥物篩選□標靶藥物□高通量藥物篩選技術(HTS)噬菌體展示技術□其他(請自填)_____
	藥物	□止痛藥□麻醉劑□血管生成□消炎□抗生素□抗體□抗癌□抗真菌□antisense□疾病模型□抗病毒□細胞凋亡□細胞訊息□中樞神經系統□藥物輸送□生育□基因治療□賀爾蒙□發炎□免疫治療□新陳代謝□天然物□病原體□胜肽□前軀藥物□蛋白質□病毒□傷口癒合□RNAi□小分子藥物幹細胞□疫苗□其他(請自填)_____
	基因體學	□allele□生物資訊學□cDNA□DNA□流行病學□EST□基因□基因型□微陣列/微陣列分析軟體□homologue□isogene□基因庫□藥物基因體學□聚合酶□多型性□定位選殖□基因轉殖動物□蛋白質體學□受體□RNA□標靶驗證□其他(請自填)_____
	研究工具	□抗體□細胞株□色層分析□細胞培養□定向分子演化□酵素□裝置□表現系統□電泳□雜交□DNA / RNA 定序□DNA / RNA 合成□老鼠模式□寡核苷酸合成□PCR 檢測□蛋白酶□試劑□RNAi□蛋白質定序□蛋白質合成□光譜□載體□其他(請自填)_____
	技術	□抗體□生物晶片□顯影劑□DNA 探針□造影成像□分子標記□放射性同位素□檢測技術□其他(請自填)_____
電資通光	電子光電	□光資訊技術□光電半導體技術□平面顯示技術□背光技術□軟性電子技術□矽基半導體技術□光學技術(含鏡片材料)□電子及光電構裝技術□電磁/光電訊號檢測□奈米電子技術□其他(請自填)_____
	資訊通訊	□有線網路□語音□資訊安全□監控□網際網路電話相關技術(VoIP) □環境控制與感知技術□Web 相關技術□智慧型資訊系統□無線通訊技術□射頻辨識技術及應用 (RFID) □電子商務□數位視/音訊與多媒體技術□光通訊技術□嵌入式系統技術□其他(請自填)_____
機能材化	材料化工	□添加劑□觸媒□塗料/塗佈□電化學□石墨烯□導電高分子□塑料/聚合/複合材料□奈米材料□化學/生物分析□半導體材料/製程□物料改質□超導體□分散均勻化□光學薄膜□石墨烯□其他(請自填)_____
	能源環工	□醫學/診斷/器械/儀器□替代/生質能源□燃料電池□化學/生物分析□高電功率□碳氫化合物□儲能□節能減碳□太陽能/電池□海洋工程□環境整治□土木工程□水利工程·□感測/量測方法/系統□其他(請自填)_____
	機械儀設	□機械元件/裝置/設備□分析儀器□光學/激光機器人□顯微技術□導航(GPS) □生理訊號感測□光譜儀□超音波□電腦輔助設計/檢測□致動器□微機電/元件/系統□環境感測/感應器□圖像處理□微控制□其他(請自填)_____

機　　密
CONFIDENTIAL

請務必填寫此附件

附件三、國立臺灣大學研究成果基本資料表

本校案號：06A-160201
(由產學合作總中心填寫)

提案日期：中華民國　105　年　2　月　18　日

一、發明名稱	中文：骨填充材 英文：Bone void filler					
二、提案人	姓名	段維新	服務單位	材料系	職稱	教授
	電話	63899	e-mail	tuan@ntu.edu.tw		
三、欲申請專利之目的(可複選)	■有意以本案為關鍵技術，新創事業，而需專利保護； □已有廠商願意技轉本案技術 / 洽談技轉事宜中； 廠商名稱 / 聯絡窗口：＿＿＿＿＿＿＿＿ 電話：＿＿＿＿＿＿＿＿ □本案之對應專利為科技產業之基礎專利(essential patent)，例如通訊產業或網際網路的通訊規格； □本技術所開發出之物品/設備，在結構上具創新性，故需專利保護，才能透過結構解析，來對照專利權之範圍，以確認是否被侵權。					
四、權利歸屬	□臺大 ■共有：與 長庚紀念醫院 共有，共有比例為 50 %：50 % (請填寫共有機構名稱)　(臺　大　：長庚紀念醫院) □其他：＿＿＿＿＿＿					

<table>
<tr><td>五、本申請案是否已公開?</td><td>※根據中華民國及美國專利法規定，凡案件於申請前已見於刊物或公開發表（含學位論文口試、學位論文電子全文及電子書目資料(含摘要)上網、學位論文紙本全文上架、學術刊物發表、學術研討會發表、媒體報導、上課講習、公開演講、參加展覽會、競賽發表…等公開事項），需於其事實發生後<u>六個月內</u>（若申請美國案為<u>12 個月內</u>）提出申請方符合申請要件。
□是(請續填以下)　□否，未來預計會公開(請續填以下)　■否
請註明公開事實及日期(若有多次公開，請條列)
(1)_____
(2)_____
※學位論文口試視同公開，若採取以下手段，則可能認為不算公開(1)口試會議不以網路公告(2)口試時聽眾不能自由進出，避免對不特定人士揭露技術(3)所有參加口試會議者(含口試者)簽署保密同意書(請提供影本一份)。
※學位論文繳交提醒：論文電子全文、電子書目資料(含摘要)及紙本論文若於網路上或圖書館供人查詢或閱覽也算是公開，若欲採取保密措施需於(1)本校電子學位論文服務系統上傳論文電子全文時，於系統上勾選<u>電子全文延後公開</u>，並另行填寫「學位論文延後公開申請書」向圖書館申請(2)<u>電子書目資料(含摘要)</u>及(3)<u>紙本論文延後公開</u>(注意：若於公開後才向圖書館申請延後公開，則仍以原公開日期為公開日)
※為維持申請專利內容之新穎性，請盡量在申請前勿公開相關內容。若已公開或預計公開請檢附已公開或預計公開之相關文件。</td></tr>
<tr><td>六、建議檢索關鍵字</td><td>中文：骨填充材料，鍶化合物，鈣化合物，燒結
英文：bone void filler, strontium compound, calcium compound, sintering</td></tr>
<tr><td>七、發明人</td><td><u>※發明人欄位填寫說明</u>:
(1)發明人超過四位時，請自行複製發明人欄位使用。
(2)發明人請填寫<u>實際的發明人</u>，參酌美國專利實務上的認定，所謂發明人必須是對發明概念之形成及至少一項申請專利範圍之標的有所貢獻之人，才能稱為發明人。美國專利法規定，若列名之發明人未有發明之事實，則不得取得專利；若發明人記載錯誤，且可證明有「欺瞞之意圖」，則此專利權無法主張權利（單純接受指示，依所設計之實驗完成實驗結果者、提出需求者、提出產品缺點者等無實質貢獻者，不能算是發明人)。
(3)未來收益分配之有功人員不限於此專利申請案所列之實際發明人。
<table>
<tr><td rowspan="5">1</td><td>姓名</td><td colspan="3">段維新 / Wei-Hsing Tuan</td></tr>
<tr><td>服務單位</td><td>國立台灣大學材料系</td><td>職稱</td><td>教授</td></tr>
<tr><td>國 籍</td><td>■中華民國 □其他：_____</td><td>身份證字號或護照字號</td><td>F121377940</td></tr>
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</table></td></tr>
</table>

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		e-mail	d01527003@ntu.edu.tw	電話	02-33661326
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		聯絡地址	桃園市龜山區萬壽路二段 1054 號		
	5	姓名	許秀菁 / Hsu, Hsiu-Ching		
		服務單位	國立台灣大學	職稱	博士後研究員
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		e-mail	d91527009@ntu.edu.tw	電話	02-33662679
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八、本申請案所屬技術領域別與可能應用範圍

本申請案所屬技術領域	醫療器材
可能應用範圍(產業或產品)	(此欄位類似於技術推廣表中的『市場與需求』) 骨填充材

※本專利應用之可行性及潛在授權廠商：

(1)本專利之技術與該國現有產品或技術之競爭性如何？

本發明意在解決目前可分解式陶瓷作為骨填充材之不足。主要技術上之差異有以下兩點：

(a) 選用材料：目前既有技術使用之材料，主要為磷酸鈣鹽和硫酸鈣，然而硫酸鈣及磷酸鈣鹽對骨缺損幫助有限。本發明使用之材料為鍶鈣化合物，因鍶元素本具有促進骨生成、抑制骨吸收的效果，因而對骨損傷處新骨的生長有所助益。

(b) 製備方法：在材料製備方面，本發明與目前相關技術差異之處為使用燒結製程。一般常用之加水結晶固化製程所製備之磷酸鈣鹽和硫酸鈣，其降解速率相較於骨之再生週期(3~6 個月)，分別有過慢(每年 5~5 %)及過快(6~8 週)的問題;此外，加水結晶固化製備之材料機械性質不佳，若崩解恐影響傷骨修復。相較之下，燒結製程製備之材料，機械強度提升，且可依燒結條件，調控材料之降解速率。

(2)依據本專利之產品或製程進入該國市場的可行性如何？

本發明之鍶鈣化合物骨填充材，係結合燒結後鍶鈣化合物之物化特性與生物相容性之優點。鍶元素具有抗骨質疏鬆的性質，且鈣化合物具有優良的生物相容性和骨傳導性，作為骨填充材已行之有年;此外，本發明選用燒結法為製備方法，以透過高溫燒結過程，提升材料之緻密化程度，達成強化機械性質之效果，且由不同之燒結溫度改變材料之相對密度，進而調控最佳降解速率。最終目的在於創造出一更符合患者術後使用之骨填充材料。

(3)若有任何公司曾與您接洽或詢問過相關技術，亦請提供。

國家/地區	**應用可行性及潛在授權廠商建議**（請列舉並以文字說明）
中華民國	
美國	

	其他	

第 15 次 討論 4050 103/06/25 (第 15 次通過)

103年度 【 硫酸鈣/生物玻璃生物複合材料之開發研究 】2年期經費核定總表

執行機構：國立臺灣大學
長庚大學

主 持 人：段維新 教授(材料科學與工程學系暨研究所)
共同主持人：蔡宗廷 助理教授(醫學系)
賴伯亮 副教授(醫學系)

年 度	業 務 費	研究設備費	國外差旅費	吳大猷獎	管 理 費	合 計	繳交報告時間 報 告 種 類
103	1,176,000	90,000	80,000	--------	171,000	1,517,000	104年5月底前 期中進度報告
104	1,176,000	150,000	80,000	--------	180,000	1,586,000	105年10月底前 期末報告
合 計	2,352,000	240,000	160,000	--------	351,000	3,103,000	
全程執行期限： 103/08/01 ～ 105/07/31			計畫編號：MOST 103-2221-E-002 -077 -MY2				

研究類型：一般型研究計畫(個別型)
研究性質：基礎研究
研究成果歸屬：國立臺灣大學
各項費用之支用請依「科技部補助專題研究計畫經費處理原則」規定辦理。

學門名稱：陶瓷

流水號：103WFA0100876
承辦人：劉春妙

※本計畫另核有博士後研究補助經費，詳見各年經費清單。

Electronic Acknowledgement Receipt

EFS ID:	24909730
Application Number:	62295013
International Application Number:	
Confirmation Number:	2114
Title of Invention:	BONE VOID FILLER
First Named Inventor/Applicant Name:	Wei-Hsing Tuan
Correspondence Address:	Wei-Hsing Tuan - Dept. of Materials Science and Engineering, National Taiwan University Taipei - 106 TW +886233663899 tuan@ntu.edu.tw
Filer:	National Taiwan University
Filer Authorized By:	
Attorney Docket Number:	
Receipt Date:	13-FEB-2016
Filing Date:	
Time Stamp:	03:54:24
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$130

RAM confirmation Number	6591
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	SB0016.pdf	472587 5fcc1c1e14e3eb6bf77cb48926b3d015bc9ab9d7	no	2
Warnings:					
This is not a USPTO supplied Provisional Cover Sheet SB16 form.					
Information:					
2	Specification	bone-void-filler-0212-2016.pdf	6121216 d79190f72832ca052e1f289c17fe25ecb95bd829	no	26
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	29436 00fe5d179cce9e1569c4d8491d915fdbf989e04d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6623239		

BONE VOID FILLER

Inventors: Wei-Hsing Tuan, Taipei (TW)
Po-Liang Lai, Taoyuan (TW)
Man-Ping Chang, Taipei (TW)
Chia-Jung Wu, Taoyuan (TW)
Hsiu-Ching Hsu, Taipei (TW)

ABSTRACT

The recovery time needed from bone defects usually takes days to even months. Many compounds are taken orally by patients to enhance bone formation. Some of these compounds are stable after heat-treating at elevated temperatures. The compounds are used as the starting material for bone void filler. The filler includes a plurality of major grains of solid solution of strontium, calcium, oxygen, sulfur and phosphorus, and a plurality of pores located at boundaries of the major grains. Inserting the filler into the location of bone defect can enhance the rate of bone formation; consequently reduce the recovery time of the patient.

FIG. 1(a)

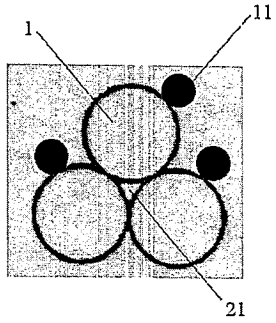


FIG. 1(b)

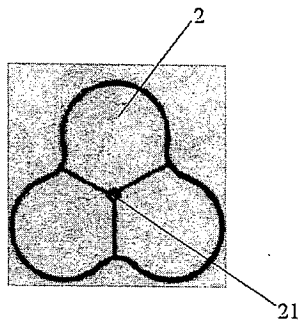


FIG. 2

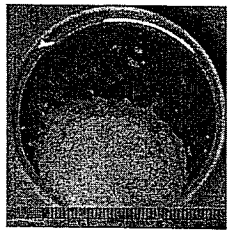


FIG. 3

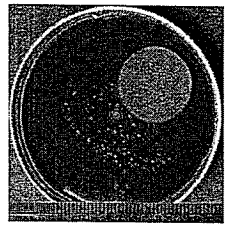


FIG. 4

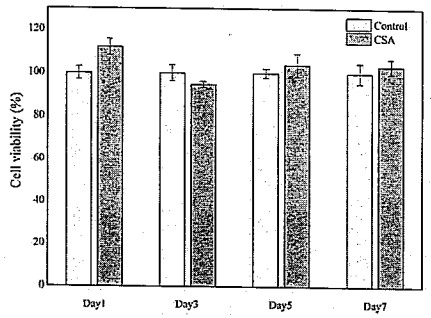


FIG. 5(a)

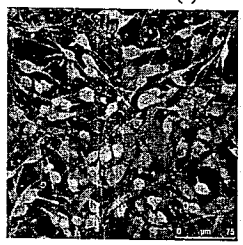


FIG. 5(b)

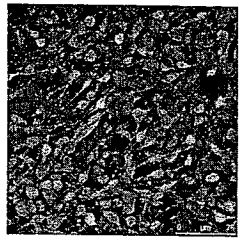


FIG. 6

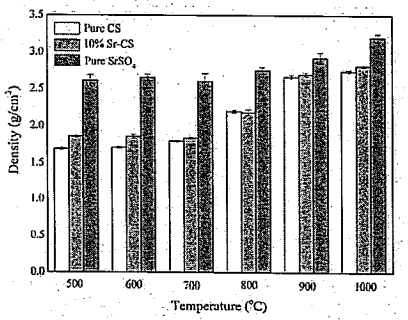

Pure CS
10% Sr-CS
Pure SrSO4
Density (g/cm3)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
500
600
700
800
900
1000
Temperature (°C)

FIG. 7

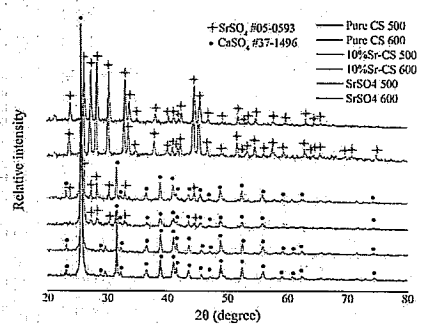

+SrSO4 #05-0593
• CaSO4 #37-1496
Pure CS 500
Pure CS 600
10%Sr-CS 500
10%Sr-CS 600
SrSO4 500
SrSO4 600
Relative intensity
20
30
40
50
60
70
80
2θ (degree)

FIG. 8

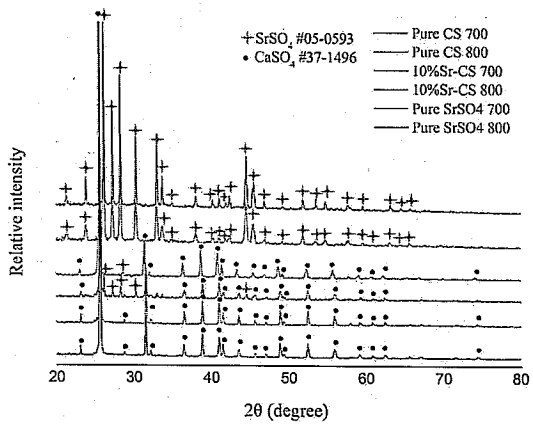

+SrSO4 #05-0593
• CaSO4 #37-1496
Pure CS 700
Pure CS 800
10%Sr-CS 700
10%Sr-CS 800
Pure SrSO4 700
Pure SrSO4 800
Relative intensity
20
30
40
50
60
70
80
2θ (degree)

FIG. 9

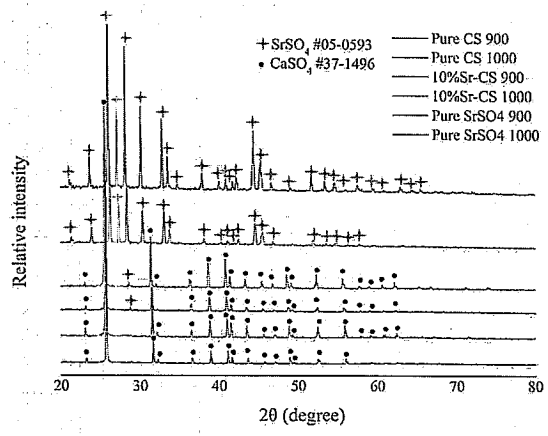

+SrSO4 #05-0593
• CaSO4 #37-1496
Pure CS 900
Pure CS 1000
10%Sr-CS 900
10%Sr-CS 1000
Pure SrSO4 900
Pure SrSO4 1000
Relative intensity
20
30
40
50
60
70
80
2θ (degree)

FIG. 10

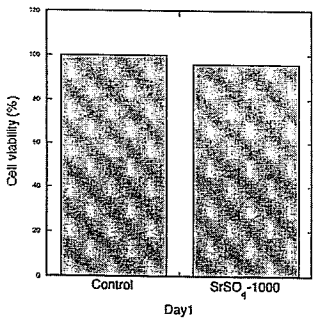


FIG. 11(a)

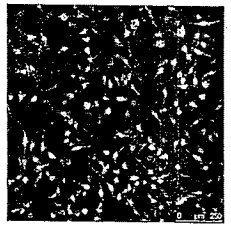


FIG. 11(b)

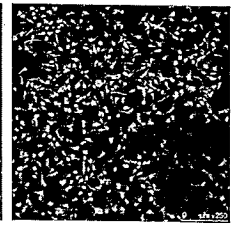


FIG. 11(c)

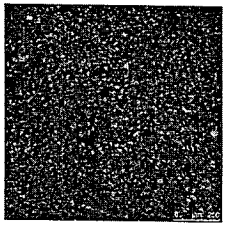


FIG. 12

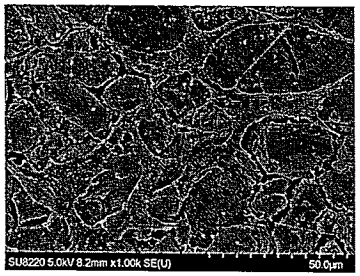

SU8220 5.0kV 8.2mm x1.00k SE(U)
50.0μm

FIG. 13

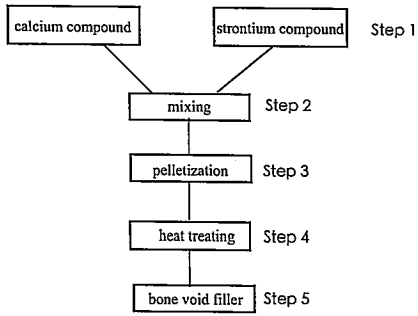

calcium compound
strontium compound
Step 1
mixing
Step 2
pelletization
Step 3
heat treating
Step 4
bone void filler
Step 5

FIG. 14

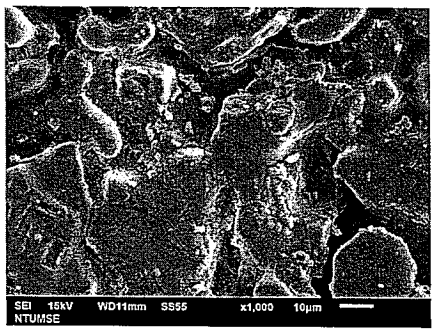

SEI 15kV WD11mm SS55 x1,000 10μm
NTUMSE

FIG. 15

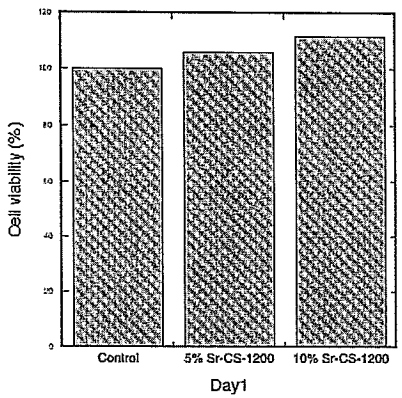
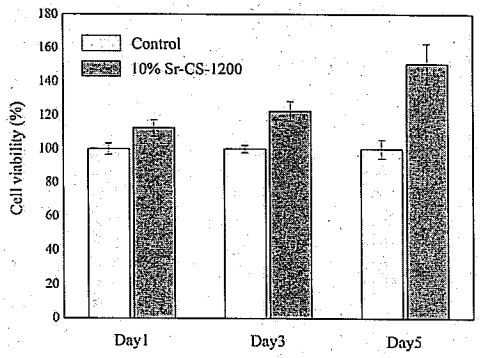

Cell viability (%)
Control
5% Sr-CS-1200
10% Sr-CS-1200
Day1

FIG. 16



BACKGROUND OF THE INVENTION

Bone void fillers are used to heal many bone-related defects, such as nonunions, delayed unions, cystic defects, arthrodesis, and skeletal defects after tumor removal or trauma etc. These bone void fillers are inserted into location of the defects. Despite the use of bone void filler, the healing of bone defects is time-consuming. Depending on the size of defects and the age of patients, the recovery time may vary from days to months. For aged persons, the recovery may even take more than 3 months. There are needs to reduce the time for the recovery from bone defects. The key to achieve such goal is lying on the growth rate of new bones.

Many medicines are available to increase the formation rate of bone, consequently reduce the recovery time from the bone defects. These medicines include calcium supplements, ergocalciferol, cholecalciferol, calcitonin, bisphosphonates, denosumab, teriparatide, strontium ranelate etc. (C-W Kuo, C-Y Hung, T-J Fang, C-F Hsieh, Taiwan Geriatrics & Gerontology, 9, 1-14, 2014). These medicines are in the form of pills or liquid, and they are taken orally or through injection on a daily basis. Though body absorbs these medicines within hours; their effects last for hours only. The time is much shorter than the time needed to recover from bone defects. After swallowing these pills into human body, they are attacked by gastric juice. Their effect on the injury bones is reduced significantly. Therefore, the patients are requested to take these pills for a long time. Days or months are still needed to heal the bone defects.

The best way to heal the bone defects is introducing the medicines directly into the location of bone defects. Since the recovery time of any bone defects is in a range of days and moths, these medicines have to stay at the location of bone defects for days or months. The key is thus lying on the long-term stability within body fluid.

SUMMARY OF THE INVESTION

Hereby, the present invention discloses stable bone void filler in terms of its stability in the body fluid. After introducing these bone void fillers into the bone defects, the filler is stable for days. The filler contains the elements from the oral-taken pills. Since the filler is stable within body fluid for days and the presence

of bone-formation elements, the use of these fillers can improve the growth rate of bones.

Many organic elements and inorganic elements are present in the bone-formation medicines (such as calcium supplements, ergocalciferol, cholecalciferol, calcitonin, bisphosphonates, denosumab, teriparatide, strontium ranelate etc.) These inorganic elements include calcium, strontium and phosphorus. Some calcium-based compounds, strontium-based compounds and phosphorus-based compounds are stable after heat-treating at elevated temperatures. For examples, the calcium sulfate can be heat treated at a temperature above 1000°C (US 8,263,513 B2, US 8,906,817 B2). The calcium sulfate pellet prepared using heat treatment is stable within human fluid for a time frame more than 28 days. The solubility of calcium sulfate, depending on the amount of crystal water) is in the range of 0.21g-0.30 g in 100 cc cold water (CRC Handbook of Chemistry & Physics). The calcium ions are releasing from the calcium sulfate bone void filler into body to enhance the formation rate of new bones.

The bisphosphonates and strontium ranelate ($C_{12}H_6N_2O_8SSr_2$) are used to treat osteoporosis. By taking bisphosphonates and strontium ranelate orally, the bone resorption becomes slower and the bone formation faster (J. Buehler, P. Chappuis, J. L. Saffar, Y. Tsouderos, A. Vignery, Bone, 29, 176-179, 2000). Though most the organic elements, such as carbon, hydrogen, and nitrogen are removed after heating to elevated temperatures, the inorganic elements, strontium, calcium and phosphorus remain. These compounds may dissolve into water slowly. For example, the solubility of strontium sulfate ($SrSO_4$) compound is 0.01 g in 100 cc cold water. The amount of soluble strontium depends strongly on the amount of surface area exposed to the water. As long as the surface area for each pellet is low, the dissolving the pellet completely can take a very long time. By controlling the amount of pores within the pellet, the solubility for each pellet within human body can be tailored. For example, the specific surface area, the surface area for each pellet, is very high as the strontium-containing compound is in its powder form, as demonstrating in FIG. 1(a). In the figure, 1 is one compound; 11 is another compound; 21 is the pore. By using heat treatment at elevated temperature, the reduction of surface area acts as the driving force to move elements into the pores between the particles, as demonstrating in FIG. 1(b). At the same time, the compounds react with each other to form solid solution. In FIG. 1(b), 12 is the solid solution forming from the reactions between

compound 1 and compound 11 at elevated temperature. The specific surface area is then reduced; consequently, the solubility of each pellet is decreased due to less availability of the free surface area.

The strontium-containing compounds can be used as the starting material, and then heat-treated at elevated temperatures to reduce the surface area of the strontium-containing pellet. With little surface area, the strontium compound is stable within body fluid for days.

The scope and the applicability of the present invention will become apparent from the detailed description given hereinafter. However, it should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will become more fully understood from the detailed description given hereinbelow and the accompanying drawings which are given by way of illustration only, and thus are not limitative of the present invention, wherein:

FIG. 1 (a) to 1 (b) respectively depicts the schematics of the pellet before and after heat treatment at elevated temperatures;

FIG. 2 depicts the morphology of the calcium sulfate hemihydrate powder pellet after soaking in Hank's solution at 37°C for 1 hour;

FIG. 3 depicts the morphology of calcium sulfate pellet after soaking in Hank's solution at 37°C for 3 days. The calcium sulfate pellet was heat treated at 1100°C;

FIG. 4 depicts the cell viability for the calcium sulfate pellet. The calcium sulfate pellets were heat treated at 1150°C. The CSA in the legend denotes the calcium sulfate.

FIG. 5 (a) to 5 (b) respectively depicts the cell morphology after 1 day and 3 days on the surface of calcium sulfate pellets. The pellets were heat treated at 1150°C;

FIG. 6 depicts the density of the calcium sulfate pellet, calcium-strontium compound pellet and strontium sulfate pellet after heat-treating at elevated temperatures; The

pure CS in legend denotes the calcium sulfate pellet; 10%Sr-CS denotes calcium-strontium compound pellet, there is 10 wt% strontium sulfate in the calcium sulfate; pure $SrSO_4$ denotes strontium sulfate pellet;

FIG. 7 depicts the X-ray diffraction patterns for the calcium sulfate pellet, calcium-strontium compound pellet and strontium sulfate pellet pellets after heat treating at 500°C and 600°C. The pure CS in legend denotes the calcium sulfate pellet; 10%Sr-CS 500 denotes calcium-strontium compound pellet heated at 500°C, there is 10 wt% strontium sulfate in the compound; $SrSO_4$ 500 denotes strontium sulfate pellet heated at 500°C;

FIG. 8 depicts the X-ray diffraction patterns for the calcium sulfate pellet, calcium-strontium compound pellet and strontium sulfate pellets after heat-treating at 700°C and 800°C;

FIG. 9 depicts the X-ray diffraction patterns for the calcium sulfate pellet, calcium-strontium compound pellet and strontium sulfate pellets after heat-treating at 900°C and 1000°C;

FIG. 10 depicts the cell viability for the strontium sulfate pellet. The strontium sulfate pellet was heat treated at 1000°C;

FIG. 11 (a) to 11 (c) respectively depicts the morphology of cells on the surface of strontium sulfate pellets after 1 day, 3 days and 7 days. The pellets were heat treated at 1200°C;

FIG. 12 depicts the morphology of the cells on the surface of strontium sulfate pellets after 1 day. The pellet was heat treated at 1200°C;

FIG. 13 depicts the flowchart for the preparation of strontium-calcium compound pellet of the present invention;

FIG. 14 depicts the surface of the strontium-calcium compound pellet. The pellet was heat treated at 1250°C;

FIG. 15 depicts the cell viability for the strontium-calcium compound pellet. The pellet was heat treated at 1200°C;

FIG. 16 depicts the cell viability for the strontium-calcium compound pellet after 1 day, 3 days and 5 days. The strontium-calcium compound pellets were heat treated at 1200°C.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be apparent from the following detailed description, which proceeds with reference to the accompanying drawing, wherein the same references relate to the same elements.

Hereinafter, the present invention will be described more clearly as follows.

EXAMPLE 1

The surface area within each pellet plays the most important role to its degradation behavior within liquid. FIG. 2 shows a pellet composing of calcium sulfate hemihydrate ($CaSO_4 0.5H_2O$) particles. The calcium sulfate hemihydrate particles are placed into a steel mode, and then an external load was applied uniaixally. A pellet composing of many calcium sulfate hemihydrate particles is prepared. The pellet collapses immediately after soaking into the Hank's solution. The composition of Hank's solution as reported by the manufacturer is shown in TABLE 1. The composition of Hank's solution is close to the composition of body fluid. It demonstrates that the pellet composing of calcium sulfate hemihydrate particles is not strong enough to resist the attack by the body fluid. The pellet thus collapses after attacking by the liquid.

TABLE 1

Additives	g/L	Additives	g/L
$CaCl_2 \cdot 2H_2O$	0.185	NaCl	8.000
$MgSO_4$	0.098	Na_2HPO_4	0.048
KCl	0.400	D-Glucose	1.000
KH_2PO_4	0.060	Phenol red sodium salt	0.011
$NaHCO_3$	0.350		

EXAMPLE 2

The problem associated to low resistance to body fluid can be improved by applying treatment at elevated temperatures. FIG 3 shows a calcium sulfate pellet after heat-treating at 1100°C for 1 hour. The calcium sulfate pellet was prepared using the same procedures as the one shown in EXAMPLE 1, except a heat treatment was applied. During the heat treatment at 1100°C, the calcium sulfate hemihydrate

changes to calcium sulfate anhydrite. The calcium sulfate anhydrite can dissolve into the body fluid slowly. However, the relative density of the calcium sulfate pellet increases to 93%. In other words, only 7% porosity remains within the pellet. With little surface area available, the pellet can survive after soaking in Hank's solution for 3 days, FIG. 3. The cell viability of the calcium sulfate pellet after heat treatment is also evaluated.

The cell viability was evaluated using preosteoblastic MC3T3-E1 cells. The cells were fed with α-minimum essential medium (α-MEM, Gibco, Life Technologies, USA), supplemented with 10% fetal bovine serum (FBS; Gibco), 100 μg/mL penicillin, 100 U/mL streptomycin, 250 ng/ml fungizone and 50 μg/ml gentamycin (Gibco). The MC3T3-E1 cells were incubated in a humidified atmosphere of 95% air and 5% CO_2 at 37°C. Extracts from calcium sulfate pellets were used in cell cultures. The pellets were dissolved in α-MEM medium at a ratio of 200 mg/ml. After 3 days, the solution was centrifuged and filtered through a 0.22 μm filter. The MC3T3-E1 cells were seeded at a density of 2×10^4 cells/well in 96-well flat-bottomed polystyrene plates (Costar 3599; Corning; USA). After 1, 3, 5 and 7 days for cell attachment, a mixture of material extracts and α-MEM was substituted for the pure cell culture medium. The volume ratio of material extract to fresh α-MEM was 1:1. Then the cells were cultured at 37°C in 5% CO_2 for three days. The test was conducted three times, each in triplicate. Cell counting Kit-8 (CCK-8; Enzo Life Sciences, USA) was used to evaluate the mitochondrial activity of the MC3T3-E1 cells; 10 ul of Kit-8 solution was added to each well. After incubation for 1 h, a microplate reader (Infinite 200 PRO, Tecan Co., Switzerland) was used to measure optical absorbance at wavelength of 450 nm. FIG. 4 shows the cell viability after 1 day, 3 days, 5 days and 7 days. The figure demonstrates that the cell viability from the extract of the heated calcium sulfate pellet is close to 100%.

The cells are also allowed to contact directly to the calcium sulfate pellet. The cell morphology after attaching to the surface of calcium sulfate pellet for 1 day and 3 days is shown in FIG. 5. The number of cell on the surface of calcium sulfate pellet after attachment for 3 days is higher than that for 1 day. It further confirms that the heat treatment improves the integrity of the pellet in body fluid, FIG. 3. The cytotoxicity of the calcium sulfate is low to cells, FIG. 4 and FIG. 5.

EXAMPLE 3

Strontium sulfate is used to demonstrate that the ability of strontium compound can survive from the treatment at elevated temperature. FIG. 6 shows the density of the strontium sulfate pellet as a function of sintering temperature. The density of strontium sulfate pellet increases with the increase of temperature for the heat treatment. At the same time, the amount of pores and the surface area for each pellet decrease with the increase of heat treatment temperature. FIG. 7 shows the X-ray diffraction patterns for the strontium sulfate pellets after heating to 500°C and 600°C for 1 hour. The strontium sulfate remains as strontium sulfate, indicating that the strontium sulfate is stable at these two temperatures. FIG. 8 shows the X-ray diffraction patterns for the strontium sulfate pellets after heating to 700°C and 800°C for 1 hour. The strontium sulfate remains as strontium sulfate, indicating that the strontium sulfate is stable at these two temperatures. FIG. 9 shows the X-ray diffraction patterns for the strontium sulfate pellets after heating to 900°C and 1000°C for 1 hour. The strontium sulfate remains as strontium sulfate, indicating that the strontium sulfate is stable at these temperatures. FIG. 7 to FIG. 9 demonstrate clearly that strontium compound is stable after the treatment at elevated temperatures.

FIG. 10 shows the cell viability from the extract of the strontium compound after 1 day. The figure demonstrates that the cell viability from the extract of the heated calcium sulfate pellet is close to 100%. FIG. 11 shows the morphology for the cells that attach to surface of strontium sulfate pellets. The strontium sulfate pellets were prepared by heating to 1200°C for 1 hour. The number of cells increases rapidly with the increase of days, indicating the proliferation of the cells with time. FIG. 12 shows one typical scanning electron micrograph to demonstrate the morphology of cells on the surface of strontium sulfate pellet. The pellet was heated at 1200°C for 1 hour. The cells are planted onto the surface of the strontium sulfate pellets for 1 day. The scanning electron micrograph demonstrates that the attachment of cells to the strontium sulfate pellet is a strong one.

EXAMPLE 4

Strontium compound can also mix with other compounds to form a solid solution composing of strontium, calcium, sulfur, phosphor and oxygen. FIG. 13 shows a flowchart to demonstrate one of the methods to prepare the bone void filler. In this

flowchart, the calcium compound is mixed with strontium compound. The calcium compound can be calcium-oxygen compounds, calcium-phosphorus compounds, calcium-sulfur compounds etc. The strontium compound can be strontium-oxygen compounds, strontium-phosphorus compounds, strontium-sulfur compounds etc. The pellets are prepared using a pelletization process, such as die-pressing process. The pellets are then heated to elevated temperatures. After heat treatment, bond void fillers in the form of pellet are obtained.

The density after heat treatment at elevated temperature can be found in FIG. 6. The density increases with the increase of temperature. In other words, the porosity remains within the pellet decreases with the increase of temperature. FIG. 14 shows one typical scanning electron micrograph for the pellet surface after heat treatment. For the pellet shown in the figure, the temperature for the heat treatment is 1250°C. From the micrograph, the amount of pores is low. The surface area of the pellet is reduced after the heat treatment.

The X-ray diffraction patterns for the strontium-calcium compound after heating to 500°C to 1000°C are shown in FIG. 7, FIG. 8 and FIG. 9, respectively. The X-ray diffraction patterns for calcium sulfate pellet are also shown in the same figure. As the amount of strontium sulfate is low, 10 wt%, the X-ray direction of the strontium-calcium compound is close to that of calcium sulfate, indicating that strontium-calcium compound is stable at the temperature interval from 500°C to 1000°C.

FIG. 15 shows the cell viability from the extract of the strontium-calcium compound after 1 day. The figure demonstrates that the cell viability increases with the increase of strontium sulfate content. FIG. 16 shows the cell viability after 1 day, 3 days and 5 days in the extracts from the strontium-calcium compound. The strontium-calcium compound was heat treated at 1200°C for 1 hour. The figure demonstrates that the cell viability increases with the increase of days. More importantly, the cell viability for the strontium-calcium compound (FIG. 16) is higher than that for the calcium sulfate pellet (FIG. 4) at the time of 5^{th} day, suggesting the presence of strontium enhances the proliferation of cells.

To sum up, the inorganic elements used in the medicines to help the formation of bones can be used to prepare bone void filler. The bone void filler can be introduced to the locations of bone defects. Through the use of heat treatment, the bone void

filler is stable within human body fluid for a longer time. The releases of the elements from bone void filler shorten the time needed to heal the bone defects.

While the invention has been described by ways of examples and in terms of preferred embodiments, it is to be understood that the invention is not limited thereto. To the contrary, it is intended to cover various modifications.