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Señor Director

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Trámite : 011

Evento : 378

Actuación : 523

Referencia : Expediente No. **13.043.214**
Asunto : Solicitud de patente: **"COMPOSICIÓN FARMACEUTICA
MICROPARTICULADA QUE COMPRENDE
ACETÓNIDO DE TRIAMCINOLONA O ANÁLOGOS
QUÍMICOS DEL MISMO, EN UNA MATRIZ DE
COPOLIMERO DE ÁCIDO POLI(LÁCTICO-CO-
GLICÓLICO)".**
Solicitante : FLEXION THERAPEUTICS, INC.
Fecha de solicitud : 4 de Marzo de 2013

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **11619** notificado por fijación en lista el 16 de Septiembre de 2014.
2. Mediante memorial del 11 de Diciembre de 2014 se solicitó oportunamente plazo para responder la acción oficial No. **11619**.
3. Mediante oficio No. **11619** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio se refieren a la claridad del título, a la claridad del pliego reivindicatorio, a la falta de unidad de invención y al nivel inventivo de las reivindicaciones 1-27 en vista de los documentos **D1: US20080248122** y **D2: US20040105821**.

"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"

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4. Respuesta a las objeciones

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

4.1. Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 7 reivindicaciones.

Con el fin de atender a la objeción hecha por el señor examinador, se solicita el cambio de título de la presente solicitud de patente a: **“COMPOSICIÓN FARMACEUTICA MICROPARTICULADA QUE COMPRENDE ACETÓNIDO DE TRIAMCINOLONA O ANÁLOGOS QUÍMICOS DEL MISMO, EN UNA MATRIZ DE COPOLIMERO DE ÁCIDO POLI(LÁCTICO-CO-GLICÓLICO)”**.

Se han introducido las siguientes modificaciones al capítulo reivindicatorio:

- Con respecto a las objeciones efectuadas a las reivindicaciones 1 y 5, que se mantienen en el nuevo pliego, las mismas fueron modificadas con el fin de precisar con mayor claridad las características técnicas de la presente invención, tal y como fue sugerido por el señor Examinador.
- Con respecto a la reivindicación 22, la misma fue modificada y corresponde a la nueva reivindicación 7, de acuerdo con las sugerencias del examinador.
- Se eliminaron las reivindicaciones originales 7-21 y 23 a 27 con lo cual las objeciones formuladas a este respecto se deben tener por superadas. Lo anterior no puede ser considerado como un desistimiento de la materia allí revelada y mi representada se reserva el derecho de volver sobre la misma durante el trámite de la presente solicitud de patente.

- Con respecto a la objeción realizada por claridad, el nuevo pliego reivindicatorio se encuentra dirigido sólo a formulaciones que comprenden (a) micropartículas de liberación controlada o sostenida que comprenden acetónido de triamcinolona (TCA), ya que se eliminaron las reivindicaciones que se encontraban dirigidas a corticosteroides.
- Tal y como fue sugerido por el señor Examinador, la expresión “aproximadamente” fue eliminada del pliego reivindicatorio.
- Con respecto a la objeción formulada a las expresiones “las micropartículas tienen un diámetro medio de entre 10µM a 100 µM” y “en donde el copolímero de ácido láctico ácido glicólico tiene una viscosidad intrínseca en el rango de 0.3 (0.35) a 0.555 dL/g”, mi representada desea poner de presente que la objeción realizada por hacer referencia a resultados a alcanzar es inadecuada, toda vez que éstos hacen referencia a parámetros, los cuales están permitidos por la legislación colombiana, tal y como lo señala el numeral 2.6.5.9 de la Guía para examen de solicitudes de patente de invención y modelo de utilidad.
- Adicionalmente, respetuosamente manifestamos que ninguna de las limitaciones en la reivindicación 1, limita el tamaño o la forma de las micropartículas cubiertas en el alcance de la misma, ni las propiedades inherentes de PLGA. Por lo tanto, la reivindicación 2 es debidamente dependiente de la reivindicación 1. Con respecto a la reivindicación 5, el rango de viscosidades inherentes abarcado por la reivindicación 1, es decir: 0,35 a 0,5 dL/g, es más amplio que el rango 0,38-0,42 dL/g reclamado por la nueva reivindicación 5.

Por lo anterior, las objeciones formuladas por el Examinador en cuanto a la claridad y concisión del pliego reivindicatorio se deben dar por superadas. En consecuencia, se solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

4.2. Argumentos con respecto a la falta de Unidad de Invención

El artículo 25 de la Decisión 486, hace referencia a:

“Artículo 25.-La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo”.

Con base a la objeción realizada por el señor Examinador, mi representada ha limitado el alcance del nuevo pliego reivindicatorio al Grupo Inventivo 1 identificado por el Examinador, que se encuentra dirigido a micropartículas de liberación controlada o sostenida que comprenden acetónido de triamcinolona (TCA) o un análogo químico o una sal farmacéuticamente aceptable del mismo. Por lo tanto, la objeción formulada a este respecto se debe tener por superada.

4.3. Argumentos con respecto a la falta de Nivel Inventivo

El artículo 18 de la Decisión 486 señala lo siguiente:

“Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”.

Una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de

manera obvia a la invención reivindicada. Adicionalmente, se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

A este respecto, respetuosamente solicitamos atentamente la reconsideración de las razones por las cuales se objeta el nivel inventivo, con base en la siguiente información:

Dado que se seleccionó el grupo inventivo 1, que se refiere a micropartículas de liberación controlada o sostenida que comprenden acetónido de triamcinolona (TCA) o un análogo químico o una sal farmacéuticamente aceptable del mismo, vale la pena resaltar que los argumentos que se presentan a continuación a favor del nivel inventivo se encuentran dirigidos al mismo.

Respetuosamente manifestamos nuestro desacuerdo con las objeciones realizadas al nivel inventivo, toda vez que ninguno de los documentos citados enseña o sugiere los rangos de combinación específicos y los elementos mencionados por la presente solicitud.

La reivindicación 1 se refiere a una formulación que comprende (a) micropartículas de liberación controlada o sostenida que comprenden acetónido de triamcinolona (TCA) o análogo químico o sal farmacéuticamente aceptable de los mismos y una matriz de copolímero de ácido poli(láctico-co-glicólico) (PLGA), en donde el TCA comprende entre 22% a 28% de las micropartículas y en donde el copolímero de PLGA tiene las siguientes características: (i) un peso molecular en el rango de aproximadamente 40 a 70 kDa; y (ii) una relación molar de lacturo:glicoluro de 80:20 a 60:40.

El señor Examinador rechazó los argumentos presentados previamente para demostrar el nivel inventivo de la presente solicitud, porque mientras los ejemplos de D1 se encuentran dirigidos a la insulina, la presente solicitud se encuentra dirigida a acetónido de triamcinolona, pero al parecer, para el Examinador esta diferencia no

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presenta ningún efecto técnico ventajoso o inesperada para las composiciones de la presente solicitud. No existe ninguna base en el arte para que el señor Examinador asegure que una persona versada en la materia se vería motivada a sustituir TCA, un corticosteroide, por insulina, que es una proteína, en las micropartículas de PLGA reveladas en los ejemplos de D1. Una persona versada en la materia no tendría ninguna razón para esperar que estos dos compuestos activos actuaran de la misma manera, dado que presentan diferentes estructuras, diferentes pesos moleculares (Insulina: 5808 g/mol y TCA: 435.5 g/mol), y diferentes propiedades químicas, elementos que sabría son suficientes para presentar una actividad significativamente distinta.

No existe ninguna enseñanza o sugerencia en ninguna de las referencias mencionadas, que indique que una simple sustitución del compuesto activo por otro pudiese ser exitosa, sin mencionar que son compuestos dispares. Por ejemplo, incluso con respecto a los otros corticosteroides ejemplificados en la presente solicitud de patente, los pesos moleculares varían en un grado mucho menor que la variación entre TCA y la insulina. Los datos presentados en los ejemplos realizados demuestran que diferentes agentes activos tienen dosis de carga únicas y específicas y proporciones molares de PLGA:

	Prednisolona	Betametasona	Propionato de Fluticasona	Fluticasona
Peso Molecular	360.4 g/mol	392.5 g/mol	444.5 g/mol	500.6 g/mol
Dosis de Carga	15% to 30%	15% to 30%	8% to 20%	8% to 20%
Ácido Láctico: Ácido Glicólico Radios Molares	60:40 to 45:55	60:40 to 45:55	60:40 to 45:55	60:40 to 45:55

A partir de un proceso experimental e investigativo, se ha encontrado con la presente solicitud micropartículas novedosas e inventivas que comprenden una dosis

específica de carga de cada uno de estos ingredientes activos y que tiene un radio molar específico de ácido láctico:ácido glicólico.

Del mismo modo, las reivindicaciones modificadas dirigidas a micropartículas de PLGA que comprenden TCA, dependientes de la reivindicación 1, específicamente requieren que las micropartículas comprendan 22% a 28% de TCA en una matriz de copolímero PLGA, en el que el PLGA tiene (i) un peso molecular en el rango de 40 a 70 kDa; y (iii) una relación molar de ácido láctico: ácido glicólico de 80:20 a 60:40. Estas relaciones se definen específicamente porque son necesarios para que una micropartícula pueda lograr el perfil de liberación deseado.

El señor Examinador menciona que D1 contiene sugerencias claras de qué tipo de polímero usar, el peso molecular del mismo, así como la relación molar de lactida: glicólido. Con todo respeto manifestamos nuestro desacuerdo, toda vez que D1 no contiene ninguna enseñanza o sugerencia de una matriz de copolímero de PLGA, en el que el PLGA tenga (i) un peso molecular en el intervalo de 40 a 70 kDa; y (iii) una relación molar de ácido láctico: ácido glicólico de 80:20 a 60:40, como es reclamado por las reivindicaciones modificadas.

Con respecto a los copolímeros de PLGA, D1 da a conocer rangos extremadamente amplios de formulaciones de copolímero donde la proporción de poli-lactida a poli-glicólido es de 100:0 a 0:100, un rango bastante general, que realmente cubre todo el universo de posibles proporciones de ácido láctico:ácido glicólico. Como se explica en la declaración de Daniel Leblanc (Anexos), las personas versadas en la técnica sabrán que los productos de copolímeros en toda la gama descrita en D1 no son posibles de formular debido a problemas con la solubilidad de los polímeros en los extremos de las proporciones. Por ejemplo, las formulaciones de copolímero de liberación de drogas parentales utilizando polímeros con una proporción de poli-lactida a poli-glicólido: de 0 a 100, no pueden ser formulados con disolventes farmacéuticamente aceptables. El único intervalo más pequeño descrito es de 90:10 a 15:85, y el único polímero PLGA ejemplificado por D1 es un copolímero de PLGA que

tiene una relación 50:50 (Ejemplo 1, párrafo [0127]). Ninguna de estas formas de realización de D1 es abarcado por la invención reivindicada.

No sólo una persona versada en la materia no tendría motivación para seleccionar el rango específico de la relación molar de ácido láctico:ácido glicólico mencionado en las reivindicaciones modificadas; si no que, además, D1 está lejos de enseñar una relación molar de ácido láctico:ácido glicólico de 80:20 a 60:40. En el párrafo [0115], D1 enseña que con los copolímeros que tienen una mayor proporción de ácido glicólico a ácido láctico se esperaría que tengan una velocidad de liberación superior como un resultado de una degradación más rápida.

Así que, basados exclusivamente en las enseñanzas del documento D1, una persona versada en la materia esperaría que una formulación de micropartículas de copolímero PLGA 50:50 tenga una degradación más rápida que las formulaciones de micropartículas de copolímero PLGA reclamadas en la presente invención. Las formulaciones reivindicadas presentan una relación de ácido láctico: ácido glicólico, pero cuando se trata de la relación de ácido glicólico a ácido láctico, las formulaciones reivindicadas tienen una relación más baja de ácido glicólico a ácido láctico, es decir, de 20:80 a 40:60, que la relación de 50:50 de D1.

En contraste con las enseñanzas de D1, los ejemplos proporcionados en la presente solicitud demuestran que una formulación de micropartículas de copolímero PLGA 50:50 no exhibió una tasa de liberación más rápida que las formulaciones de micropartículas reivindicadas que tienen una relación molar de ácido láctico: ácido glicólico de 80: 20 a 60:40 (Tabla 5, la Tabla 10 y Figura 19). En particular, la Figura 19 demuestra que el uso de PLGA 50:50 no mejoró la cinética de liberación del corticosteroide: acetónido de triamcinolona (TCA) en comparación con la formulación de PLGA 75:25. Además, **las formulaciones de micropartículas que tienen 25% TCA en PLGA 50:50, liberaron TCA a un ritmo más lento y dio una liberación incompleta en comparación con la cantidad equivalente de TCA incorporado en PLGA 75:25.**

Asimismo, D1 presenta una amplia gama de posibles pesos moleculares de los polímeros en el párrafo [0115], que van desde 1 kD a 1.000 kD. De hecho, D1 enseña que la elección del peso molecular de los polímeros "no está particularmente limitado" en el párrafo [0115]. Basado en las enseñanzas en D1, la persona versada en la materia no tendría ninguna razón objetiva u otra motivación para seleccionar los intervalos específicos de peso molecular de los copolímeros mencionados por las reivindicaciones modificadas, o cualquier expectativa de obtener el perfil de liberación exhibido por las partículas reclamadas.

Además, D1 también da a conocer una amplia gama de contenido del compuesto activo en peso del 50% o menos (Párrafo [0106]), pero basados en esta enseñanza, no hay ninguna razón objetiva u otra evidencia que motivaría a una persona versada en la materia a seleccionar la dosis de carga específica entre 22% a 28% como se ha indicado en el pliego reivindicatorio de la presente solicitud. Los únicos ejemplos en D1 indican que la concentración de proteína de las microesferas descritas, es decir, el ingrediente activo, fue del 14%, que está por debajo del intervalo reivindicado del ingrediente activo (Párrafos [0128] - [0129]).

Por lo tanto, es claro que las micropartículas reclamadas no están descritas en su totalidad, ni son sugeridas por D1, y los datos mencionados en el capítulo descriptivo son suficientes para apoyar la conclusión de que las formulaciones de micropartículas reclamadas muestran **resultados sorprendentes e inesperados** que podrían no haberse previsto con base a las enseñanzas de D1, y que como bien lo menciona la "GUÍA PARA EXAMEN DE SOLICITUDES DE PATENTE DE INVENCION Y MODELO DE UTILIDAD" de su despacho en el numeral 2.13.5.3.1, está reconocido como un indicio de nivel inventivo. Por consiguiente, se le debe otorgar una compensación a mi representada que demuestra nuevos hechos (efectos sorprendentes e inesperados) a las enseñanzas descritas en el estado de la técnica y contribuyen con el desarrollo de la tecnología.

El señor Examinador aborda las deficiencias de D1 citando D2. Sin embargo, una persona versada en la materia que pretende producir formulaciones de

micropartículas de liberación controlada o sostenida, no tendría ninguna razón objetiva para utilizar las enseñanzas de D2, ya que no da a conocer micropartículas de liberación controlada o sostenida de ningún tipo. De hecho, D2 enfatiza repetidamente que las formulaciones descritas, preferiblemente liberan una mayoría del agente farmacéutico encapsulado de las micropartículas a las 24 horas después de la administración (Resumen, párrafos [0010], [0029], [0044], [0140] y reivindicaciones 2, 3, 19, 20, 31, 34, 41, y 42). En consecuencia, una persona versada en la materia no habría sido motivada para combinar las enseñanzas de D1 y D2.

Además, D2 describe también rangos extremadamente amplios de los componentes de micropartículas y agentes activos, pero no hay evidencias objetivas que llevarían a un experto en la materia a los intervalos reivindicados. Por ejemplo, en los párrafos [0064] a [0077], D2 enumera una multitud de materiales potenciales de matriz, incluyendo PLGA, pero no hay ninguna revelación a un rango adecuado la relación molar de ácido láctico:ácido glicólico en las micropartículas de PLGA. De hecho, los ejemplos incluyen PLGA, pero no revelan el peso molecular o la relación molar de ácido láctico:ácido glicólico de los copolímeros utilizados. Por lo tanto, no hay razón laguna para que una persona versada en la materia seleccionara los rangos específicos de peso molecular y relación molar de ácido láctico: ácido glicólico mencionados por las reivindicaciones modificadas.

Asimismo, en el párrafo [0138], D2 enseña que el contenido del agente farmacéutico en las micropartículas está generalmente, entre aproximadamente 1 y aproximadamente 70% en peso, y en realizaciones típicas, el agente farmacéutico está presente en una cantidad entre el 5 y el 50% en peso. Por lo tanto, no hay ninguna razón u otra evidencia que motivaría a la persona versada en la materia a seleccionar la dosis de carga específica entre el 22% y el 28% de TCA, como la presente solicitud.

Por lo tanto, las referencias citadas, solas o en combinación, no describen o sugieren los elementos específicos de las formulaciones de TCA reivindicadas. Como tal, no hay ninguna razón u otra evidencia proporcionada por las enseñanzas de D1 y D2 que llevarían el experto en la materia a la invención reivindicada. En consecuencia,

se pone de presente que las formulaciones de micropartículas TCA reclamadas por las reivindicaciones modificadas no son obvias a la vista de los documentos citados y el estado de la técnica en el momento de presentación de la solicitud. Esto es apoyado por la amplitud de los intervalos descritos en D1 y D2, y la especificidad de los intervalos reivindicados, que se encuentran suficientemente lejos de los rangos revelados en los ejemplos de D1 y D2. Las diferencias son claras cuando los perfiles de liberación obtenidos por medio de la invención reivindicada se comparan con los ejemplos de D1.

En la presente invención se reclaman rangos específicos de dosis adecuadas de carga, pesos moleculares de copolímeros de PLGA, y relaciones molares de lactida:glycolida. Las dosis de carga probadas y los pesos moleculares de PLGA utilizados en los ejemplos están dentro de estos intervalos reivindicados y las micropartículas que satisfacen la limitación de la relación molar de lactida:glycolido de PLGA exhibieron la cinética de liberación deseada. Con base a lo anterior, es claro que los rangos reivindicados y la cinética deseada no son enseñados o sugeridos por D1, D2 o su combinación.

Respetuosamente señalamos, que dado a las objeciones realizadas por el examinador en cuanto a la falta de datos, estuviere ignorando los datos presentados en la solicitud y los argumentos presentados por dos expertos en la materia, como lo son el Doctor LeBlanc y el Doctor Kumar, presentados como adjuntos en la respuesta anterior, y adjuntados nuevamente en la presente.

Las formulaciones de micropartículas TCA reclamados no habrían sido obvias para el experto en la materia debido a que, como se explicó anteriormente, muestran resultados sorprendentes e inesperados. Por lo tanto, la combinación específica de elementos e intervalos mencionados por la presente solicitud no son sólo optimización de rangos. Dado que características como la velocidad de liberación y la velocidad de degradación dependen en gran medida el agente activo específico utilizado, se seleccionaron estos rangos específicos, ya que proporcionan un perfil de liberación sostenida deseado, a saber, la capacidad de entregar TCA a niveles terapéuticos

sostenidos sin supresión del eje hipotalámico-pituitario-adrenal (HPA) durante al menos 14 días. Las formulaciones de micropartículas con este perfil de liberación deseado han sido demostradas en estudios clínicos para proporcionar un efecto analgésico clínicamente significativo, por ejemplo, alivio del dolor, durante todo el estudio de 12 semanas, y este efecto es una mejora significativa sobre una suspensión inyectable aprobada de TCA (IR TCA). Un resumen de estos resultados se muestra en el Resumen #2668 presentado en el 2013 por el Colegio Americano de Reumatología-Reunión Científica Anual, presentado con la respuesta a la acción oficial anterior. Además, la declaración de Anjali Kumar, Ph.D., FAHA, un inventor llamado de la presente solicitud, demuestran que las formulaciones de micropartículas de TCA que se encuentran fuera de los intervalos reivindicados no presentan este perfil de liberación deseado.

Por ejemplo, la declaración Kumar demuestra que las formulaciones de micropartículas de PLGA utilizando una dosis de carga de TCA que fue menor que el intervalo reivindicado, de 22% a 28%, exhibía un perfil de liberación lenta con una liberación significativa acumulada menor por más de 28 días que la formulación reivindicada, mientras que las formulaciones de micropartículas de PLGA que tiene una dosis de carga de 40%, mostraron un perfil de liberación más rápido, con más del 80% de la TCA siendo liberada por 7 días después de la administración.

Además, la Declaración Kumar demuestra que las formulaciones de micropartículas hechas con un copolímero de PLGA que tiene una relación de ácido láctico a ácido glicólico fuera del intervalo reivindicado, es decir de 80:20 a 60:40, exhiben varias propiedades indeseables. Por ejemplo, las formulaciones de micropartículas hechas usando un copolímero de PLGA 50:50, liberan TCA a un ritmo más lento y tienen una liberación incompleta en comparación con la cantidad equivalente de TCA incorporado en una micropartícula hecha usando un copolímero PLGA 75:25 (es decir, dentro de la relación molar reclamada por las reivindicaciones modificadas). Además, las formulaciones de micropartículas hechas con el copolímero de PLGA 50:50 también mostraron una fase sustancial de retraso, con muy poca o ninguna TCA están siendo liberados después de 7 días, que continuaron hasta

aproximadamente el día 50. Por último, la Declaración Kumar demuestra que se encontró que las formulaciones de micropartículas hechas usando un copolímero PLGA 75:25 que tienen un peso molecular menor que el intervalo reivindicado de 50-54 kDa, presentan una tasa de liberación de TCA más lenta y una liberación incompleta de TCA.

Con base a los argumentos presentados previamente, donde queda claro que los documentos D1 y D2, no revelan en su totalidad las características técnicas reivindicadas en la presente invención y que la materia reclamada si presenta un efecto técnico sorprendente que no habría sido posible deducir con base a la técnica anterior, es claro que posee la altura inventiva necesaria para que se le conceda el privilegio solicitado.

4.4 Concesión de Solicitudes equivalentes

Si bien entendemos y aceptamos que cada país es autónomo en la concesión o negación de los privilegios de patente, queremos resaltar el hecho que el análisis de los requisitos para el otorgamiento de esos derechos es prácticamente universal. La presente invención fue concedida por la Oficina de Patentes de Estados Unidos, patente No. 8,828,440 y por la Oficina de Patentes de Sudáfrica, patente No. 2013/00831.

A este respecto, deseamos poner de presente que si bien cada país es autónomo de conceder o negar una solicitud luego de la realización del estudio de fondo, es claro que el hecho de que la novedad y el nivel inventivo de una invención hayan sido reconocidos por varias oficinas a nivel mundial, es un indicio de la patentabilidad de la misma toda vez que (i) el estudio de novedad y nivel inventivo en todas las Oficinas de Patentes del mundo es realizado por personas con conocimientos técnicos en el área de interés que son consideradas personas idóneas para emitir conceptos sobre la patentabilidad de una invención y que (ii) los resultados de los exámenes de novedad o de patentabilidad efectuados respecto a solicitudes extranjeras pueden ser reconocidos como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención, tal como se señala en el artículo 46 de la Decisión 486:

“Artículo 46.- La oficina nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan

opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial.

De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina:

a) copia de la solicitud extranjera;

b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera;

(...)

*La oficina nacional competente podrá **reconocer los resultados de los exámenes referidos en el literal b) como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención***" (Negrilla fuera del texto).

4.5 Conclusión

Por todo lo anterior, el documento D1, el documento D2, o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la invención de la presente solicitud.

Por lo tanto, consideramos que el Examinador está pasando por alto que una sola diferencia con respecto al estado de la técnica, permite concluir que el objeto reivindicado es nuevo. Además, está excluyendo el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

5. Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 11619, toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto

el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

6. Anexos

- Nuevo pliego reivindicatorio conformado por 7 reivindicaciones.
- Declaración de Anjali Kumar.
- Declaración de Daniel Leblanc.
- Resumen #2668 presentado en el 2013 por el Colegio Americano de Reumatología- Reunión Científica Anual.
- Patente US 8828440.

Señor Director,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

mem
COLO-20037-0841-001-9
CPT\CPT\ID-275791\WPC20037
No. M-2014-275791\CPT

REIVINDICACIONES MODIFICADAS

1. Una formulación que comprende (a) micropartículas de liberación controlada o sostenida que comprenden acetónido de triamcinolona (TCA) o análogo químico o sal farmacéuticamente aceptable del mismo y una matriz de copolímero de ácido poli(láctico-co-glicólico) (PLGA), en donde el TCA comprende entre 22% a 28% de las micropartículas y en donde el copolímero de PLGA tiene las siguientes características: (i) un peso molecular en el rango de 40 a 70 kDa; y (ii) una relación molar de lacturo:glicoluro de 80:20 a 60:40.
2. La formulación de la reivindicación 1, en donde las micropartículas tienen un diámetro medio de entre 10 μm a 100 μm .
3. La formulación de la reivindicación 1, en donde el copolímero de PLGA tiene una relación molar de ácido láctico: ácido glicólico de 75:25.
4. La formulación de la reivindicación 1, en donde el TCA comprende una dosis de carga total de TCA entre 10 a 50 mg.
5. La formulación de la reivindicación 1, en donde el copolímero de ácido láctico-ácido glicólico tiene una viscosidad intrínseca en el rango de 0.38 a 0.42 dL/g.
6. La formulación de la reivindicación 1, en donde las micropartículas comprenden adicionalmente una unidad estructural de polietilenglicol

(PEG), en donde la unidad estructural de PEG comprende entre 25% a 0% porcentaje en peso de la micropartícula.

7. Un proceso de obtención para fabricar la formulación de la reivindicación 1, en donde las micropartículas se fabrican utilizando un proceso de evaporación de solvente, utilizando por lo menos un aparato de secado por aspersión, aparato de lecho fluido o un disco giratorio, en donde el TCA se dispersa en una solución orgánica de copolímero de ácido láctico-ácido glicólico y la mezcla se trata para retirar el solvente de la mezcla, produciendo por lo tanto micropartículas.

CPT\CPT\ID-275790\WPC20037

APPENDIX E

Via EFS

Date of Deposit: February 7, 2014

Attorney Docket No. 41022-501C01US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Neil Bodick et al.	CONFIRMATION NUMBER	4020
SERIAL NUMBER:	13/422,994	EXAMINER:	T. Kassa
FILING DATE:	March 16, 2012	ART UNIT:	1619
TITLE:	CORTICOSTEROIDS FOR THE TREATMENT OF JOINT PAIN		

DECLARATION OF ANJALI KUMAR, Ph.D, FAHA UNDER 37 C.F.R. §1.132

I, Anjali Kumar, Ph.D., FAHA, declare and state that:

1. I have reviewed the contents and the file history for the above-identified application.
2. I am the Vice President, Nonclinical R&D and Scientific Affairs at Flexion Therapeutics, Inc., the assignee of the instant application, and I have been working in the biopharmaceutical industry for over 18 years in all aspects of drug discovery, pharmacology, nonclinical and clinical development, project management and regulatory submissions. I have my Ph.D. from Georgia Institute of Technology in Chemical Engineering (Bioengineering). I am the author of numerous peer-reviewed publications in the biopharmaceutical field, and I have published many articles, presentations, Abstracts and posters in the fields of corticosteroid microparticle formulations and intra-articular inflammation.
3. I have reviewed the latest Office Action in the above-identified application. I understand that the pending claims are rejected under 35 U.S.C. § 103(a) for being unpatentable over U.S. Patent Application Publication No. 2008/0248122 by Rashba-Step *et al.* ("Rashba-Step") in combination with U.S. Patent Application Publication No. 2004/0105821 by Bernstein *et al.* ("Bernstein").
4. I have reviewed the accompanying amendment and the above-referenced application in conjunction with the cited references. I make this declaration to rebut the Examiner's assertions with which I do not agree. For the reasons discussed below, it is my opinion that the claims as presented in the instant response are not rendered obvious in view of

the cited references, and the claimed microparticle formulations provide unexpected advances over the state of the art at the time the instant application was filed.

5. The claimed microparticle formulations fulfill an unmet need in the field of pain and/or inflammation therapies. Optimal injectable treatment of pain and/or inflammation therapies is hindered by the inadequate efficacy (magnitude and/or duration). The claimed microparticle formulations are effective in slowing, arresting, reversing or otherwise inhibiting structural damage to tissues associated with progressive disease with minimal prolonged suppression of the HPA axis and/or other long term side effects of corticosteroid administration.
6. The claimed microparticle formulations address this critical unmet need in pain and/or inflammation therapy. The claimed PLGA copolymer microparticles encapsulate triamcinolone acetonide (TCA), and enable the gradual release of TCA over an extended period of time. These claimed microparticle formulations maintain a therapeutically relevant concentration of TCA for an extended period of time so that increased magnitude and/or duration of efficacy can be achieved.
7. The studies shown in the working examples provided in the instant application demonstrate that the claimed microparticle formulations encapsulate TCA, release active TCA *in vivo* at a desired sustained-release profile, namely sustained therapeutic levels, *e.g.*, in the joint, without adverse suppression of the hypothalamic-pituitary-adrenal (HPA) axis for at least 14 days.
8. The claimed microcapsule formulations have a specific set of characteristics – namely, a corticosteroid load dose between 22% to 28% of the microparticles; a PLGA copolymer having (i) a molecular weight in the range of about 40 to 70 kDa; and (ii) a lactide:glycolide molar ratio of 80:20 to 60:40.
9. The working examples demonstrate that microparticle formulations that include combinations of TCA load dose and PLGA characteristics that fall outside of the claimed ranges do not exhibit the desired characteristics such as, for example, TCA release rate, TCA release profile, TCA load efficiency, and/or impact on the HPA axis.

10. Example 4 of the instant application demonstrates that varying the load dose of TCA (% by weight) affects the *in vitro* release profile of the TCA-PLGA microparticle formulation (*see e.g.*, Table 5, Table 8 and Figure 17). Corticosteroid microparticle formulations having a corticosteroid load does that fell outside of the claimed range of 22-28% load dose did not exhibit the desired release profile.
11. In particular, the microparticle formulations that included 10%, 15% or 20% TCA in the PLGA microparticle formulation exhibited a slower release profile, with a significant less cumulative release over 28 days than the claimed formulation, which includes TCA at load dose between 22% to 28% by weight. For example, the 10% TCA-containing PLGA microparticle formulations exhibited less than 20% cumulative release; the 15% TCA-containing PLGA microparticle formulations exhibited less than 30% cumulative release; and the 20% TCA-containing PLGA microparticle formulations exhibited less than 55% cumulative release. In addition, a depot formulation containing 40% TCA by weight exhibited a faster release profile, with greater than 80% of the triamcinolone released by day 7 post-administration.
12. Microparticle formulations having a copolymer ratio of lactic acid to glycolic acid that fell outside of the claimed range of 80:20 to 60:40 did not exhibit the desired release profile. Example 4 provides data demonstrating that varying the ratio of lactic acid to glycolic acid in the PLGA copolymer affects the *in vitro* release profile of the TCA-PLGA microparticle formulation (*see e.g.*, Table 5, Table 10 and Figure 19).
13. In particular, Example 4 provides studies in which the claimed microparticle formulations, which use a lactic acid:glycolic acid ratio of 75:25, were compared to a PLGA copolymer with a lactic acid:glycolic acid ratio of 50:50. Contrary to what would have been expected from the literature and state of the art at the time this application was filed¹, the use of PLGA 50:50 did not improve the release kinetics of the triamcinolone acetone as compared to the PLGA 75:25, as shown in Figure 19. Moreover,

¹/ For example, the Rashba-Step reference teaches at paragraph [0115] that PLGA formulations having a higher ratio of poly-glycolide to polylactide in the polymer have a faster degradation rate. Thus, the skilled artisan would have expected a 50:50 PLGA copolymer microparticle formulation to have a faster degradation rate than the claimed copolymer microparticle formulations, which have a lower ratio of glycolic acid to lactic acid.

microparticle formulations having 25% TCA in PLGA 50:50 released the corticosteroid at a slower rate and gave an incomplete release as compared to the equivalent amount of TCA incorporated in PLGA 75:25. The PLGA 50:50 formulation also exhibited a substantial lag phase, with little or any TCA is being released after 7 days, which continued to about day 50.

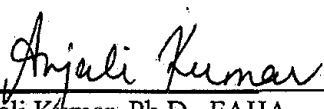
14. Furthermore, microparticle formulations having a lactic acid-glycolic acid copolymer with a molecular weight that fell outside of the claimed range of 40 to 708 kDa did not exhibit the desired release profile. Example 4 also demonstrates that varying the molecular weight of the PLGA used in the 75:25 copolymer formulation affects the *in vitro* release profile of the TCA-PLGA microparticle formulation (*see e.g.*, Table 5, Table 9 and Figure 18).
15. In particular, this example provides studies in which the claimed microparticle formulations, which use 75:25 PLGA with molecular weight of 50-54 kDa, were compared to microparticle formulations made using 75:25 PLGA with a molecular weight of 29kDa. Figure 18 demonstrates that the use of lower molecular weight PLGA (29 kDa) did not improve the release of TCA from the microparticles, and moreover, the rate of TCA release decreased and was incomplete as compared to higher molecular weight PLGA of the claimed microparticle formulations.
16. Thus, it is my opinion that the precise range of TCA load dose and the exact composition (molecular weight and lactide:glycolide molar ratio) of the PLGA polymer recited by the claimed microparticle formulations, is patentable because this specific combination produces sustained-release TCA microparticles formulations that release TCA at sustained therapeutic levels, for example, in the joint, without adverse suppression of the HPA axis for at least 14 days to at least 90 days following injection into a joint.
17. As such, the claimed microparticle formulations provide unexpected advances over the state of the art by exhibiting a desirable sustained-release profile, namely a sustained-release profile where TCA is released over a period of time of at least 14 days. These microparticles fulfill an unmet need in the field of pain and/or inflammation therapies by

increasing the amount of time a subject is exposed to TCA without having to increase the dosage of TCA administered.

18. Finally, without acquiescing to the Examiner's rejections, I submit, as a skilled artisan in the field of microparticles and microparticle formulations, that even if a certain combination of microparticle characteristics (*e.g.*, the lactide:glycolide molar ratio of the microparticle copolymers, the copolymer molecular weight, the load percentage of the biological molecule, the inherent viscosity of the microparticle and so on) were deemed to be "obvious to try," one could not reasonably predict that any specific combination would successfully produce microparticles that exhibit the desired release profile, load efficiency, and/or clinical efficacy. Moreover, the skilled artisan would not be able to reasonably predict whether microparticles having that specific combination of characteristics could be successfully reduced to practice by one of ordinary skill in the art. The ability to identify an optimal set of microparticle characteristics in conjunction with the appropriate manufacturing procedure for producing the desired microparticle formulation is not a mere optimization of ranges. The claimed microparticles in this application have been shown to successfully and reproducibly exhibit the desired release kinetics, high load efficiency and high clinical efficacy, where other previous microparticle formulations have failed.
19. In conclusion, the cited references, Rashba-Step and Bernstein, alone or in combination, do not disclose or suggest microparticle formulations that have the specific combination of corticosteroid, *e.g.*, TCA, load dose and PLGA characteristics and that exhibit a sustained-release profile where the corticosteroid is released at sustained therapeutic levels, *e.g.*, in the joint, without adverse suppression of the hypothalamic-pituitary-adrenal (HPA) axis for at least 14 days. Accordingly, I believe that the microparticle formulations recited by the amended claims submitted herewith are not obvious in view of the teachings in Rashba-Step and/or Bernstein.

U.S.S.N.: 13/422,994
Bodick et al.

20. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.



Anjali Kumar, Ph.D., FAHA

Signed this 7th day of February 2014

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APPENDIX D

Conclusion: The fast-track pathway leads to a reduction in irreversible sight loss and is associated with reduced diagnosis and treatment costs. It results in 2.6 QALY's gained for each patient that does not suffer sight loss, suggesting that the fast-track pathway is more cost effective than the conventional pathway for management of early GCA. The ICER of implementing the fast-track pathway is $\leq$ 1,950 per QALY with an average cost saving to the NHS of $\leq$ 925 for each patient. Our results do not include the small educational/refresher costs and are preliminary but indicate that the Fast track GCA pathway should be 'rolled out' globally.

Disclosure: K. Achilleos, None; P. Pntil, None; W. W. Maw, None; L. Bown, None; D. Halsall, None; C. Dobson, None; C. DeJaco, None; P. Borg, None; S. Gupta, None; B. Dargupta, None.

ACR Concurrent Abstract Session
Osteoarthritis I: Therapeutics in Osteoarthritis
Tuesday, October 29, 2013, 2:30 PM-4:00 PM

2668

A Randomized, Double-Blind, Dose Ranging Study Comparing FX006, An Intra-Articular (IA) Sustained-Release Formulation Of Triamcinolone Acetonide (TCA), To An Approved Injectable Suspension Of TCA In Patients With Osteoarthritis (OA) Of The Knee. Neil Bodick¹, Joelle Lufkin¹, Christina Willwerth¹, Pierre Lachance², Gregory Jasey³, Anil Gupta⁴, Anthony Chris⁵, Marc Russo⁶, Michael O'Mahony⁷, Sam Hencin⁸, Louise Murdoch⁹, Ferdinandus de Looze¹⁰, David Hunter¹¹ and Michael Clayman¹. ¹Flexion Therapeutics, Burlington, MA, ²Clinique St-Louis (Recherche) Inc, Quebec, QC, ³North Walkerville Orthopaedic Associates, Windsor, ON, ⁴Anil K. Gupta Medicine Professional Corporation, Toronto, ON, ⁵Alm Health Group, Waterloo, ON, ⁶Hunter Clinical Research, Broadmeadow, Australia, ⁷London Road Diagnostic Clinic and Medical Centre, Sarnia, ON, ⁸SKDS Research Inc., Newmarket, ON, ⁹Emcorius Research, Malvern East, Australia, ¹⁰AusTrials Pty Limited, Sherwood, Australia, ¹¹Royal North Shore Hospital, St. Leonards, Australia.

Background/Purpose: FX006 is a novel sustained-release formulation of TCA in poly(lactic-co-glycolic) acid microspheres intended to maintain therapeutic concentrations in the joint up to 3 months following IA injection. In patients (pts) with OA of the knee, FX006 was compared to an approved injectable suspension of TCA (TCA IR) to identify a dose of FX006 to move forward into Phase 3.

Methods: Pts with baseline average daily pain intensity (ADP) of $\geq$ 5 to $\leq$ 9 on an 11 point Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (pain as bad as you can imagine) were randomized (1:1:1:1) and treated with a single IA injection of FX006 (containing 10, 40 or 60 mg of TCA) or 40 mg of TCA IR. Pts were evaluated at 7 visits over 12 wks for efficacy, safety and PK. Primary endpoint: change from Baseline to each of Wks 8, 10 and 12 in the weekly mean of ADP. Secondary endpoints: time to onset of pain relief, WOMAC (pain, stiffness and function), responder status, and global impression of change.

Results: Pts (228) were randomized and treated (FX006 10 mg, n=58, FX006 40 mg, n=59, FX006 60 mg, n=60; TCA IR, n=51). Treatment arms were well balanced across demographic and baseline characteristics (mean baseline ADP: 6.5). FX006 40 mg was superior to TCA IR on weekly mean of ADP at Wk 5 to Wk 10 ($p<0.05$) (average pain reduction -0.9) (Figure 1). The 40 mg dose also demonstrated significant improvement over TCA IR ($p<0.05$) in secondary outcomes at Wk 8 (Table 1). Time to onset of pain relief was the same for FX006 40 mg and TCA IR. The 10 mg dose produced effects that were consistently improved relative to TCA IR but of lesser magnitude than those of the 40 mg dose. The 60 mg dose did not produce an improvement relative to the 40 mg dose. There were no related SAEs. AEs were generally mild and unrelated to study drug. Local knee-related AEs, lab assessments, ECGs and vital signs were unremarkable and similar across all treatments. Plasma PK across the FX006 doses were linear and dose-dependent. Peak plasma concentrations achieved with TCA IR were 10 $\times$ of that seen with FX006 40 mg.

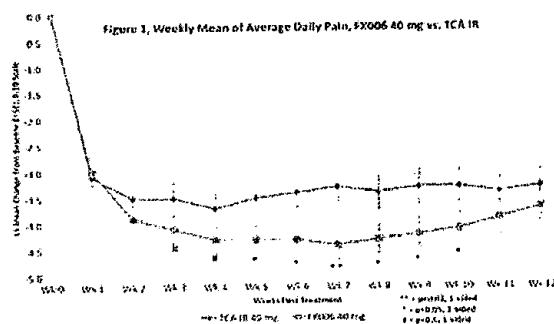


Table 1. Secondary efficacy endpoints at Week 8 comparing FX006 40 mg vs. TCA IR 40 mg

	FX006 40 mg (n=59)	TCA IR 40 mg (n=51)
WOMAC A (pain) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.33 (0.098)	-0.96 (0.108)
LSMD vs TCA IR (90% CI)	-0.37 (-0.61, -0.13)	
1 sided p-value	0.0058	
WOMAC A1 (pain on walking) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.2 (0.12)	-0.8 (0.13)
LSMD vs TCA IR (90% CI)	-0.4 (-0.7, -0.1)	
1 sided p-value	0.0098	
WOMAC B (stiffness) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.49 (0.112)	-0.99 (0.124)
LSMD vs TCA IR (90% CI)	-0.49 (-0.77, -0.22)	
1 sided p-value	0.0018	
WOMAC C (function) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.31 (0.096)	-0.94 (0.106)
LSMD vs TCA IR (90% CI)	-0.37 (-0.61, -0.14)	
1 sided p-value	0.0049	
OMERACT-OARSI ^a		
n (%)	53 (89.8%)	32 (69.0%)
p-value	0.0118	
OR (90% CI)	3.9 (1.6, 9.3)	
Responder $\geq$ 30% improvement ^b		
n (%)	47 (85.5%)	27 (62.8%)
p-value	0.0119	
OR (90% CI)	3.5 (1.5, 7.9)	
PGIC (1-7 Likert scale)		
LSM change from baseline (SE)	1.8 (0.16)	2.6 (0.17)
LSMD vs TCA IR (90% CI)	-0.7 (-1.1, -0.3)	
1 sided p-value	0.0013	
CGIC (1-7 Likert scale)		
LSM change from baseline (SE)	1.8 (0.16)	2.6 (0.17)
LSMD vs TCA IR (90% CI)	-0.7 (-1.1, -0.3)	
1 sided p-value	0.0013	

a n=59 for FX006 40 mg; n=46 for TCA IR
b n=55 for FX006 40 mg; n=43 for TCA IR
LSM = least squares mean; LSMD = least square means difference; WOMAC = Western Ontario and McMaster Osteoarthritis Index; OMERACT-OARSI = Outcome Measures in Rheumatoid Arthritis Clinical Trials- Osteoarthritis Research Society International; PGIC = Patient Global Impression of Change; CGIC = Clinical Global Impression of Change

Conclusion: In pts with OA of the knee, the 40 mg dose of FX006 demonstrated an amplified and prolonged therapeutic effect relative to TCA IR. A Phase 3 study of the 40 mg dose of FX006 is being planned.

Disclosure: N. Bodick, Flexion Therapeutics, 1, Flexion Therapeutics, 3; J. Lufkin, Flexion Therapeutics, 1, Flexion Therapeutics, 3; C. Willwerth, Flexion Therapeutics, 1, Flexion Therapeutics, 3; P. Lachance, None; G. Jasey, None; A. Gupta, None; A. Chris, None; M. Russo, None; M. O'Mahony, None; S. Hencin, None; L. Murdoch, None; F. de Looze, None; D. Hunter, None; M. Clayman, Flexion Therapeutics, 1, Flexion Therapeutics, 3.

APPENDIX C

Via EFS

Date of Deposit: February 7, 2014

Attorney Docket No. 41022-501C01US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Neil Bodick et al.	CONFIRMATION NUMBER	4020
SERIAL NUMBER:	13/422,994	EXAMINER:	T. Kassa
FILING DATE:	March 16, 2012	ART UNIT:	1619
TITLE:	CORTICOSTEROIDS FOR THE TREATMENT OF JOINT PAIN		

DECLARATION OF DANIEL LEBLANC UNDER 37 C.F.R. §1.132

I, Daniel Leblanc, declare and state that:

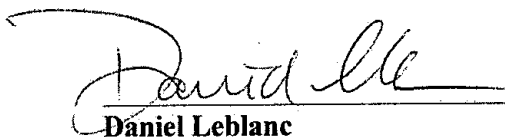
1. I have reviewed the contents and the file history for the above-identified application.
2. I have a bachelor's degree in Chemical Engineering from Syracuse University and a Master's in Technology Management from the University of Pennsylvania School of Engineering and the Wharton School. I have been working in the pharmaceutical industry for 18 years, 14 of which have been working directly on novel drug delivery systems with a focus on PLGA-based drug delivery systems. During this time, I have participated in gaining FDA approval for Nutropin Depot® (micronized particles of recombinant human growth hormone embedded in polylactide-coglycolide microspheres), Risperdal® Consta® (extended-release microsphere formulation of a psychotropic drug), Vivitrol® (microsphere formulation of naltrexone), Exanatide SR, as well as worked on several other PLGA and non-PLGA based systems for parenteral injections as well as pulmonary applications. I have worked with regulatory agencies worldwide on comparability strategies for scale up and development of novel drug delivery systems.
3. I have reviewed the latest Office Action in the above-identified application, USSN 13/422,994 ("the '994 application"). I understand that the pending claims are rejected under 35 U.S.C. § 103(a) for being unpatentable over U.S. Patent Application Publication No. 2008/0248122 by Rashba-Step *et al.* ("Rashba-Step") in combination with U.S. Patent Application Publication No. 2004/0105821 by Bernstein *et al.* ("Bernstein").

4. I have reviewed the accompanying amendment and the above-referenced application in conjunction with the cited references. I make this declaration to rebut the Examiner's assertions with which I do not agree. For the reasons discussed below, it is my opinion that the ranges disclosed in Rashba-Step, particularly the range of ratios for poly-lactide to poly-glycolide copolymers, are so broad as to encompass a substantial number of embodiments that are not just inoperable, but are actually impossible to formulate.
5. Rashba-Step discloses extremely broad ranges of copolymer formulations where the ratio of poly-lactide to poly-glycolide is from 100:0 to 0:100 – a range that actually covers the entire universe of possible lactic acid: glycolic acid ratios. However, those skilled in the art would appreciate that copolymer products in the full range described in Rashba-Step are not possible to formulate into injectable, parenteral dosage forms due to problems with the solubility of polymers at the extremes of the ratios. For example, polymers with of poly-lactide to poly-glycolide ratio of 0:100 can only be solubilized in highly fluorinated solvents, rendering parenteral formulations impracticable due to the hazardous with the solvents. Alternate technologies, such as melt extrusion or film casting, while possible for implantable devices, are not suited for injection into the synovium due to the shape and size of the particle. At both extremes of poly-lactide or poly-glycolide in these formulations, challenges would also exist due to the poor solubility of either of these individual components in aqueous solution, keeping the polymer within the body for significantly extended times (upwards of a year in the case of 100% poly-lactide), failing to allow for a desirable sustained release formulation.
6. Rashba-Step and Bernstein focus on formulation of microparticles designed for pulmonary delivery of the drug product, covering intended durations of release of hours to days, while the microparticle formulations claimed in the '994 application target much longer durations of release. Those skilled in the art would know that to achieve orders of magnitude longer release profiles, the techniques and steps elucidated in Rashba-Step and/or Bernstein are not pertinent to the extended release profiles targeted by the corticosteroid microparticle formulations of the '994 application. In addition, the combination of (i) the size of the claimed particles in the '994 application (i.e., 10-70 micron) compared to those disclosed in

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Rashba-Step and/or Bernstein (i.e., sub 10 micron), (ii) the design of the drug product in the '994 application, namely uniformly dispersed active pharmaceutical ingredient (API) in a solid microparticle, versus the "core and shell" approach described in Rashba-Step and Bernstein, and (iii) the specific range of drug loading dose of the claimed corticosteroid microparticle formulations in the '994 patent (i.e., 22-28%), taken together, all create a unique system in the '994 application as compared to those discussed in Rashba-Step and/or Bernstein, and the broad stroke descriptions provided by these references are not appropriate for use in the claimed formulations of the '994 application.

7. In conclusion, the ranges taught by Rashba-Step are so unreasonably broad that the skilled artisan could not formulate copolymer microparticles at all disclosed ranges given the inherent characteristics of the polymers used, let alone corticosteroid microparticle formulations that exhibit a controlled or sustained-release profile. Accordingly, I believe that the microparticle formulations recited by the amended claims submitted herewith are not obvious in view of the teachings in Rashba-Step.
8. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.


Daniel Leblanc

Signed this 7th day of February 2014



(12) **United States Patent**
Bodick et al.

(10) **Patent No.:** **US 8,828,440 B2**
(45) **Date of Patent:** **Sep. 9, 2014**

(54) **CORTICOSTEROIDS FOR THE TREATMENT OF JOINT PAIN**

(75) Inventors: **Nell Bodick**, Boston, MA (US); **Robert C. Blanks**, Auburndale, MA (US); **Anjali Kumar**, Belmont, MA (US); **Michael D. Clayman**, Gloucester, MA (US); **Mark Moran**, Orinda, CA (US)

(73) Assignee: **Flexion Therapeutics, Inc.**, Burlington, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/422,994**

(22) Filed: **Mar. 16, 2012**

(65) **Prior Publication Data**

US 2012/0288534 A1 Nov. 15, 2012

Related U.S. Application Data

(63) Continuation of application No. 13/198,168, filed on Aug. 4, 2011, now abandoned.

(60) Provisional application No. 61/370,666, filed on Aug. 4, 2010.

(51) **Int. Cl.**
A61K 9/14 (2006.01)
A61K 9/50 (2006.01)
A61K 31/56 (2006.01)
A61K 31/573 (2006.01)
A61K 9/00 (2006.01)
A61K 9/16 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 9/1647** (2013.01); **A61K 31/573** (2013.01); **A61K 9/0024** (2013.01); **A61K 9/0019** (2013.01); **A61K 9/1641** (2013.01); **A61K 9/1694** (2013.01)
USPC **424/489**; **424/497**; **514/181**

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — David J Blanchard
Assistant Examiner — Tigabu Kassa
(74) **Attorney, Agent, or Firm** — Cooley LLP

(57) **ABSTRACT**

Corticosteroid microparticle formulations are provided for use for treating pain, including pain caused by inflammatory diseases such as osteoarthritis or rheumatoid arthritis, and for slowing, arresting or reversing structural damage to tissues caused by an inflammatory disease, for example damage to articular and/or peri-articular tissues caused by osteoarthritis or rheumatoid arthritis. Corticosteroid microparticle formulations are administered locally as a sustained release dosage form (with or without an immediate release component) that results in efficacy accompanied by clinically insignificant or no measurable effect on endogenous cortisol production.

10 Claims, 30 Drawing Sheets

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FIG. 1

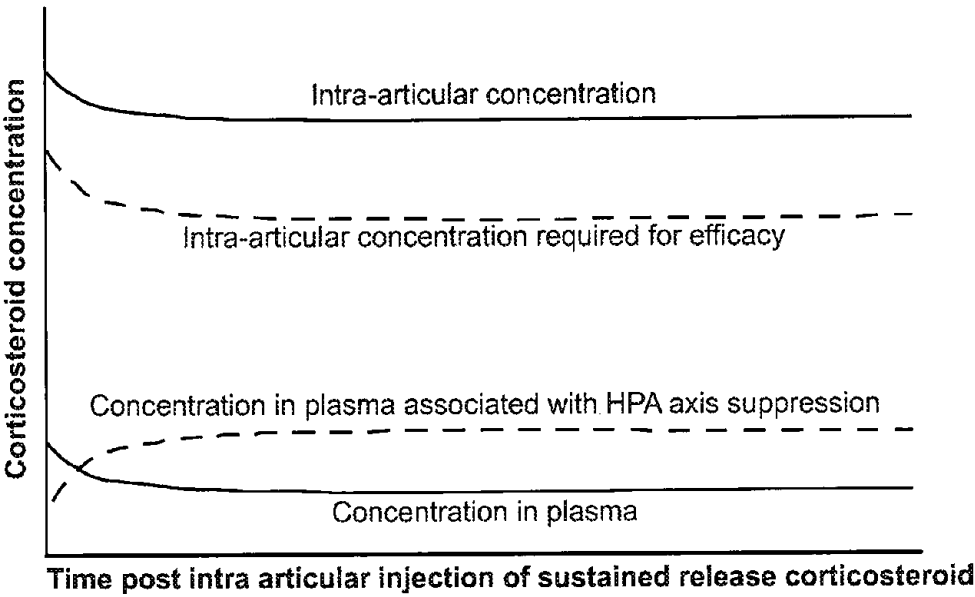
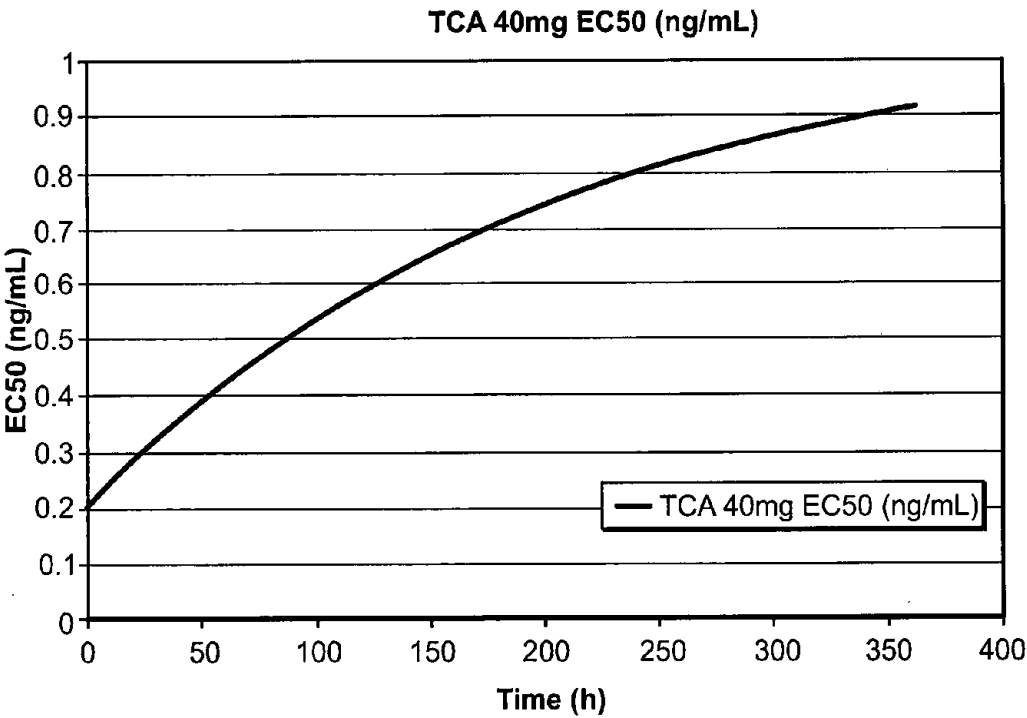


FIG. 2



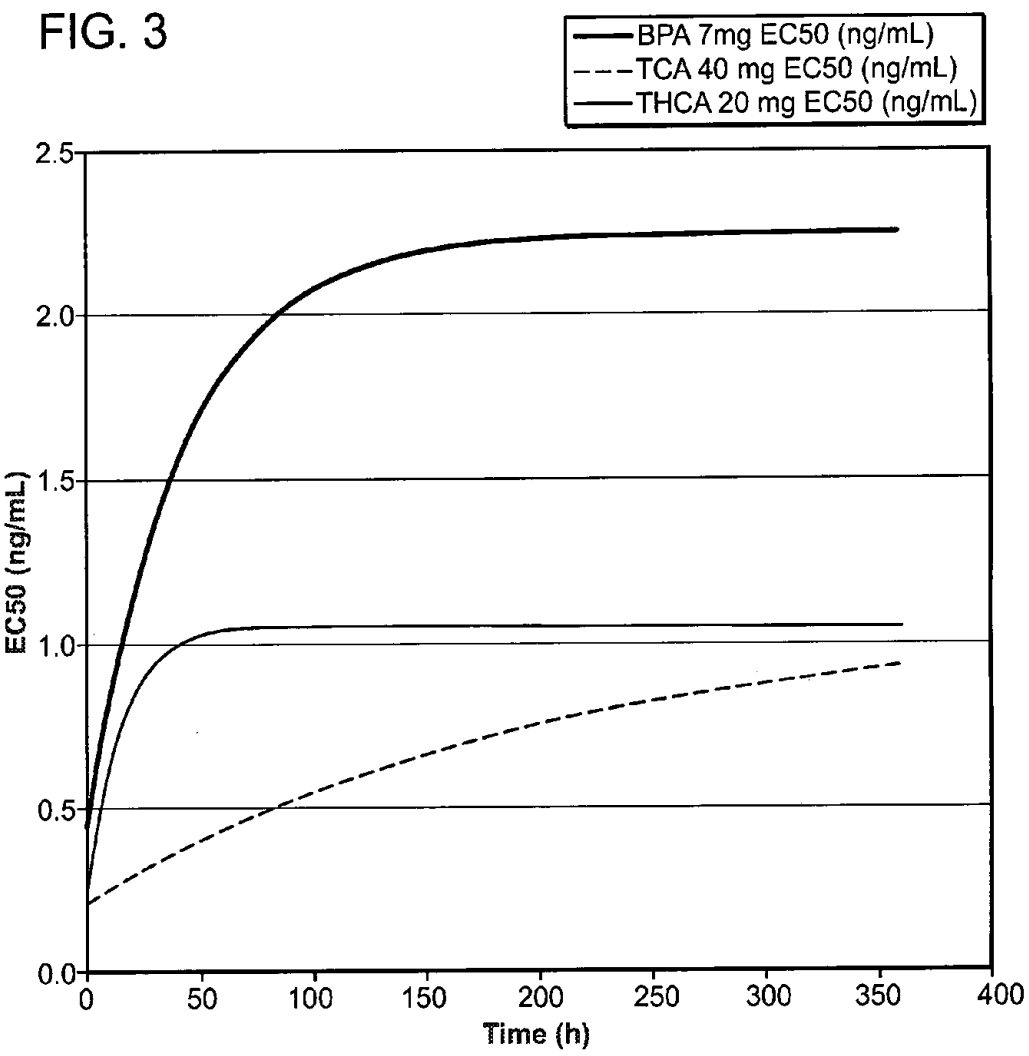


FIG. 4A

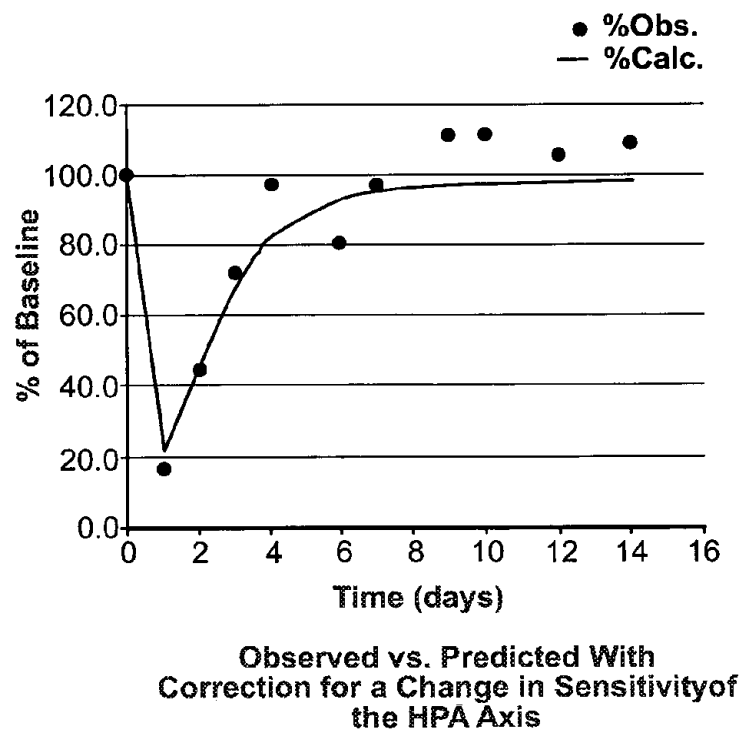
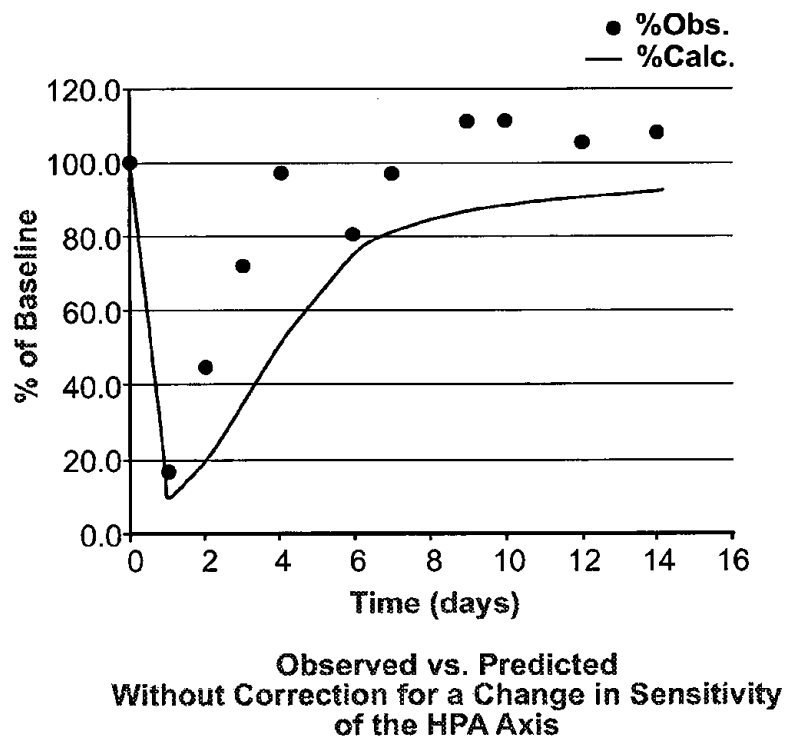
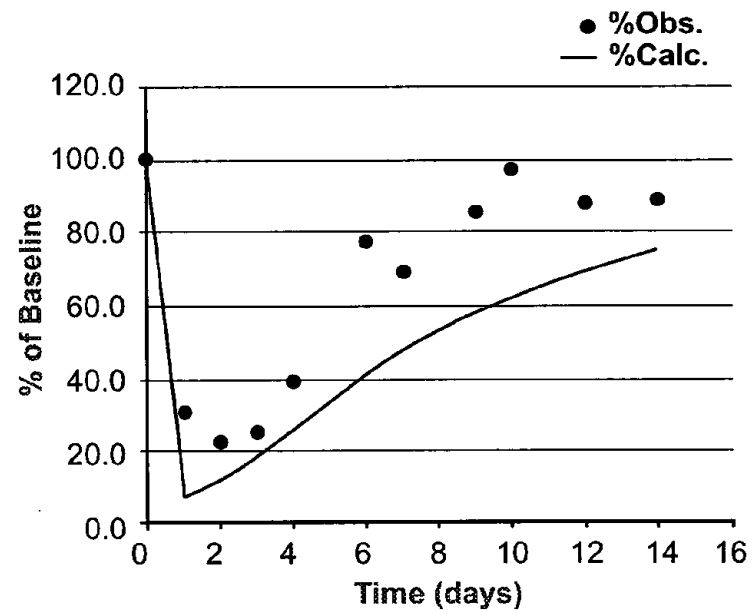
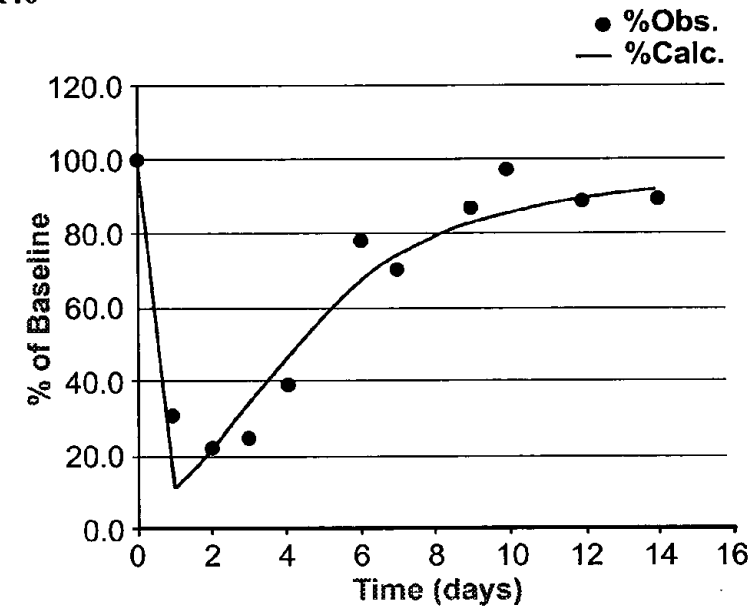


FIG. 4B



Observed vs. Predicted
Without Correction for a Change in Sensitivity
of the HPA Axis



Observed vs. Predicted With
Correction for a Change in Sensitivity
of the HPA Axis

FIG. 4C

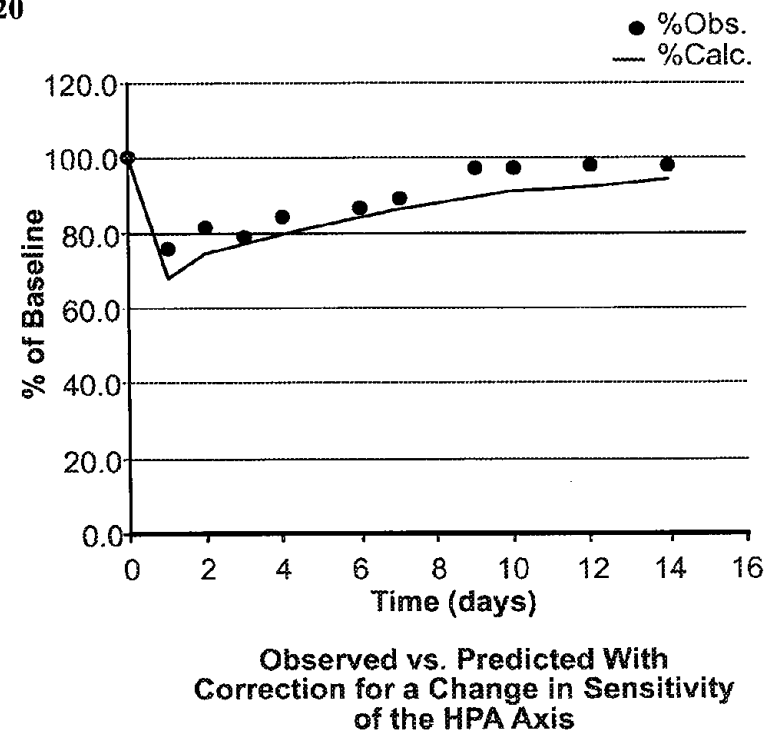
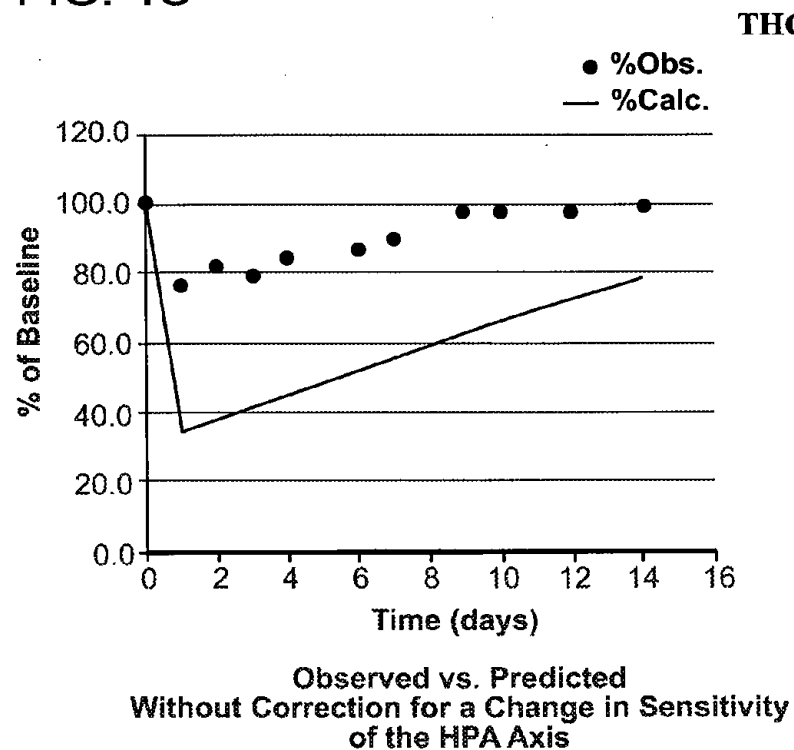


FIG. 5

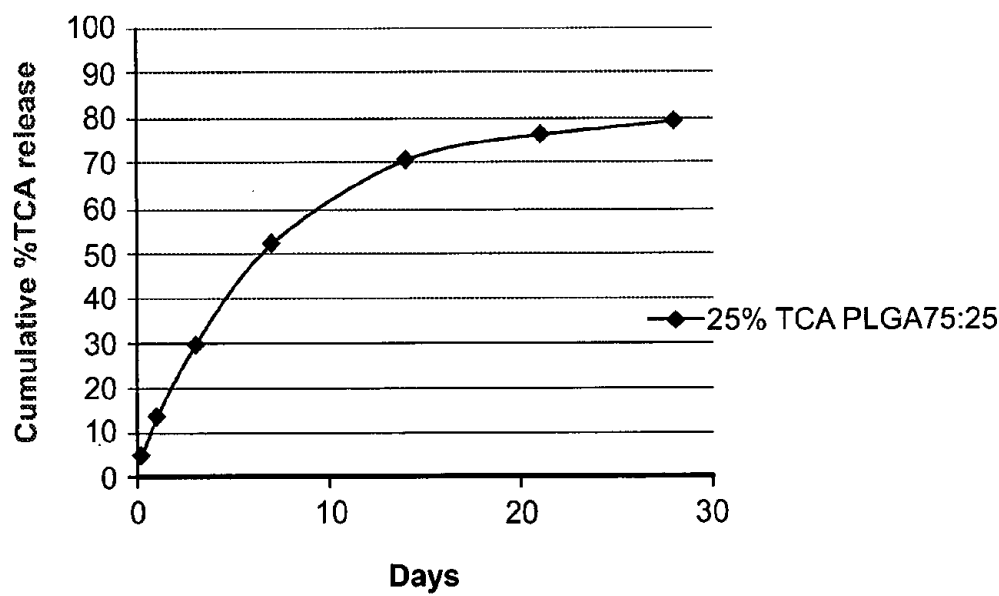


FIG. 6

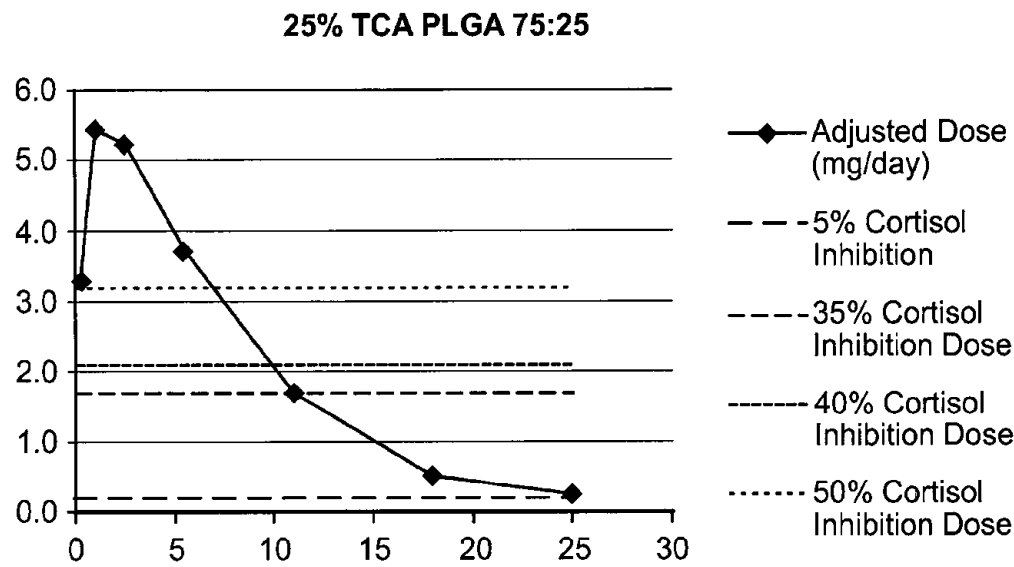


FIG. 7

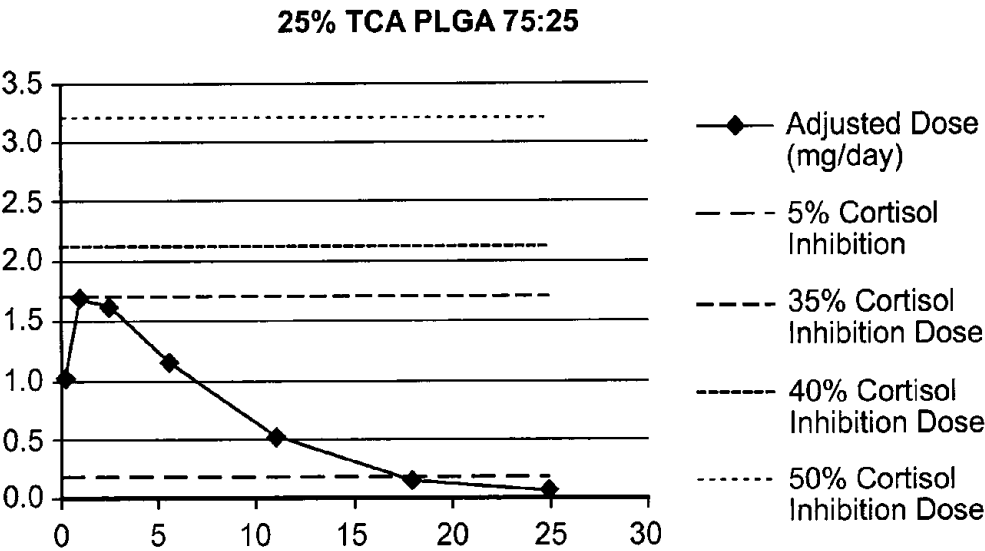


FIG. 8

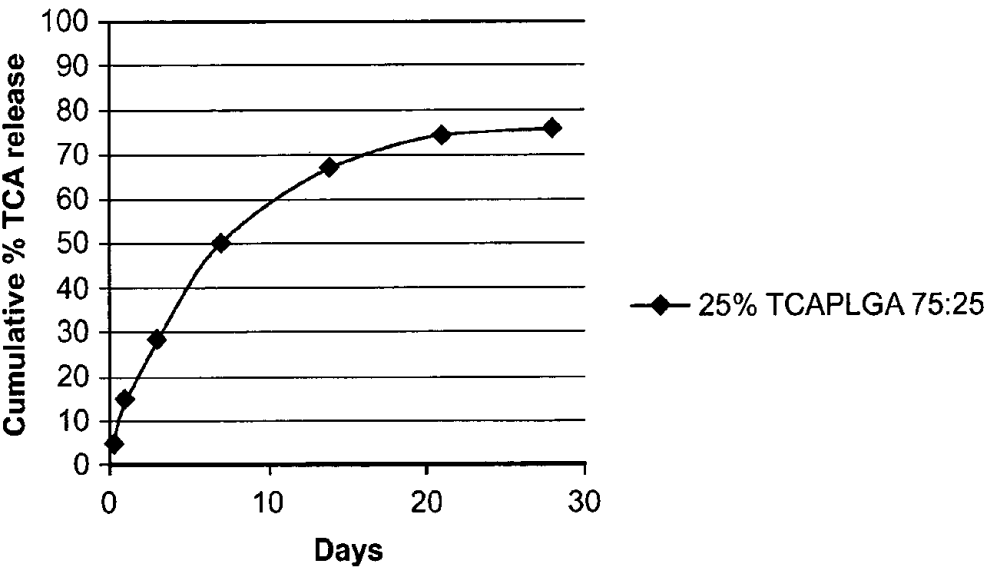


FIG. 9

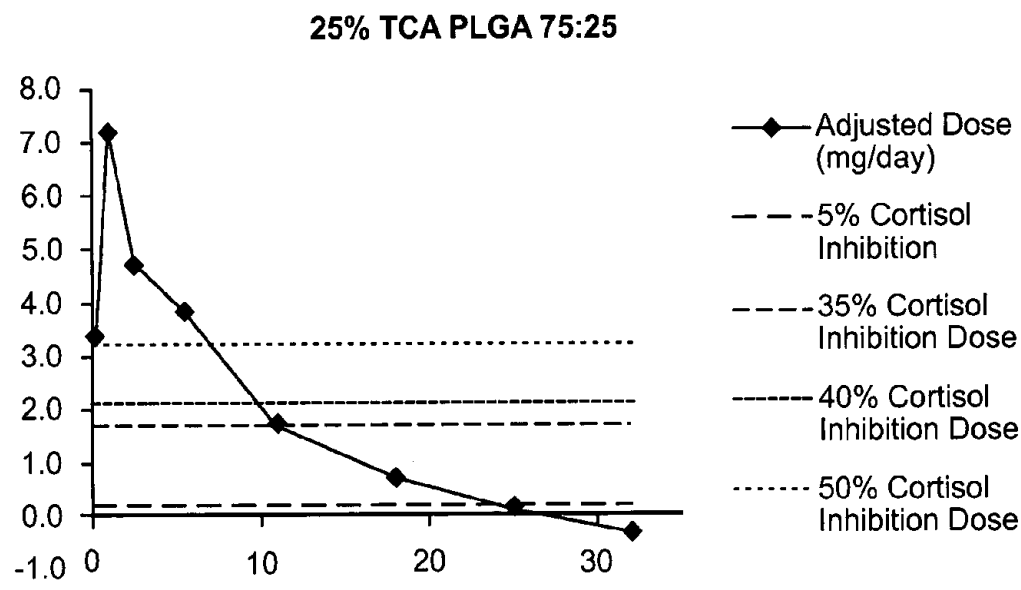


FIG. 10

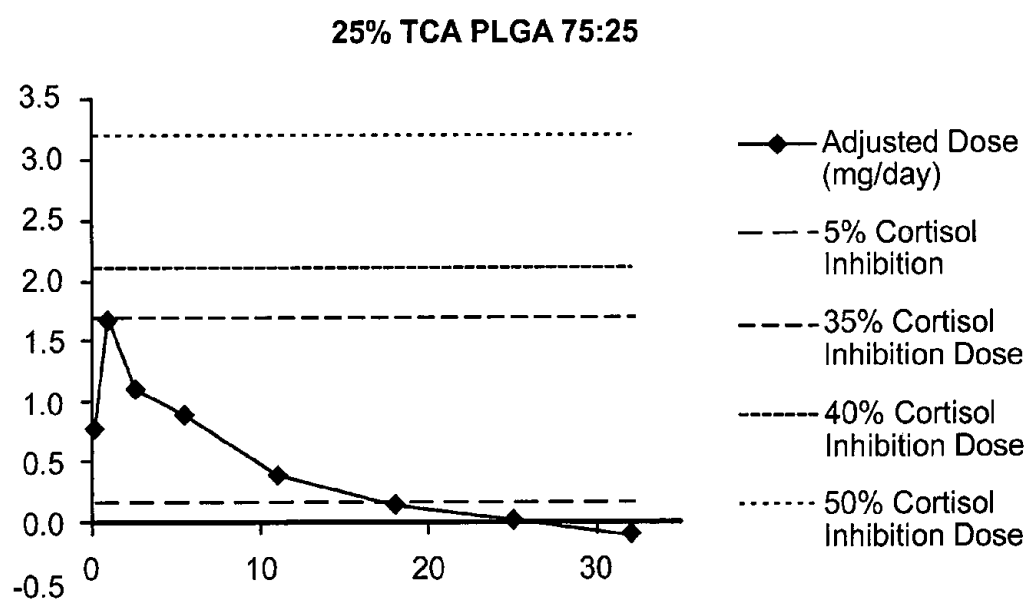


FIG. 11

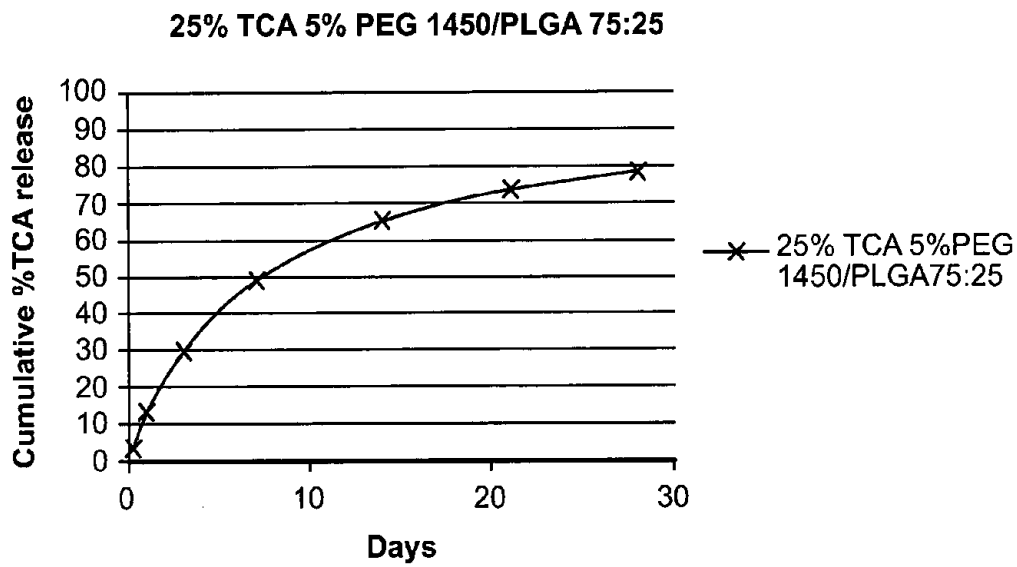


FIG. 12

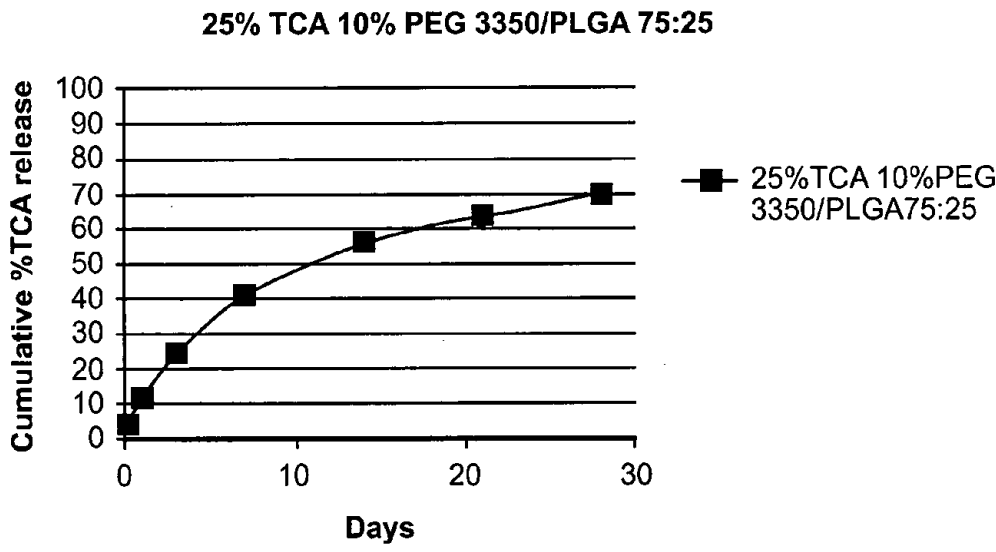


FIG. 13

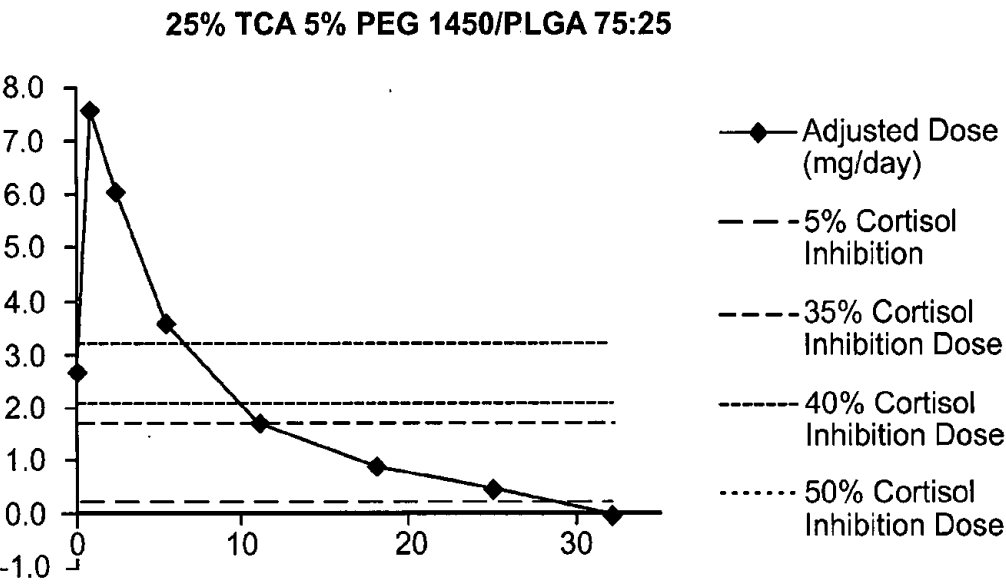


FIG. 14

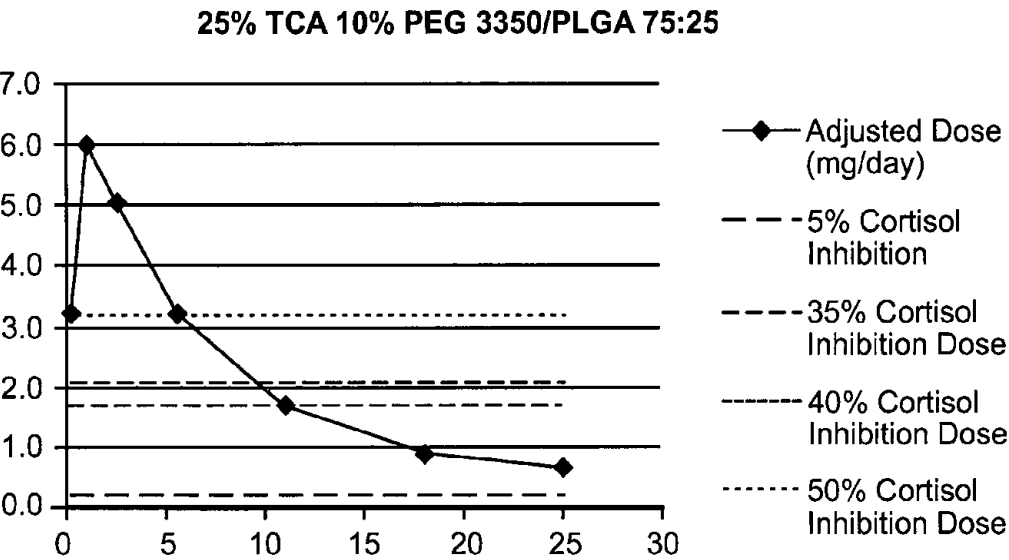


FIG. 15

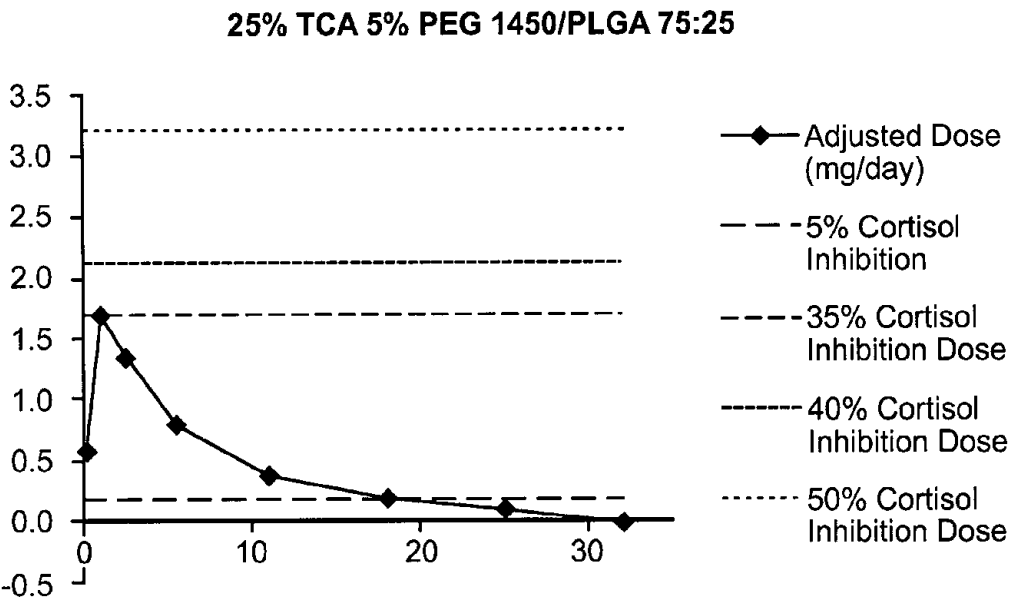


FIG. 16

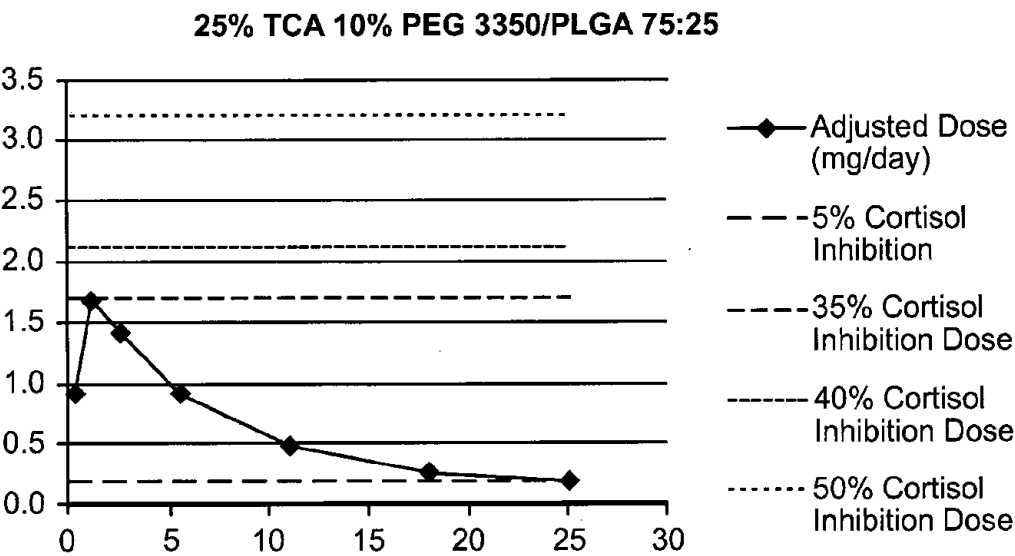


FIG. 17

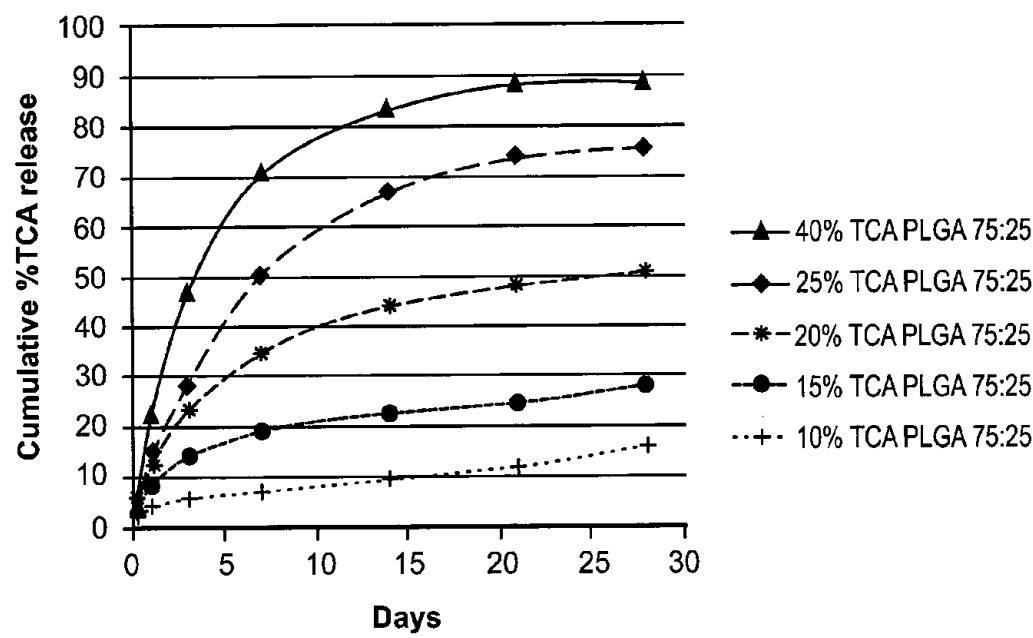


FIG. 18

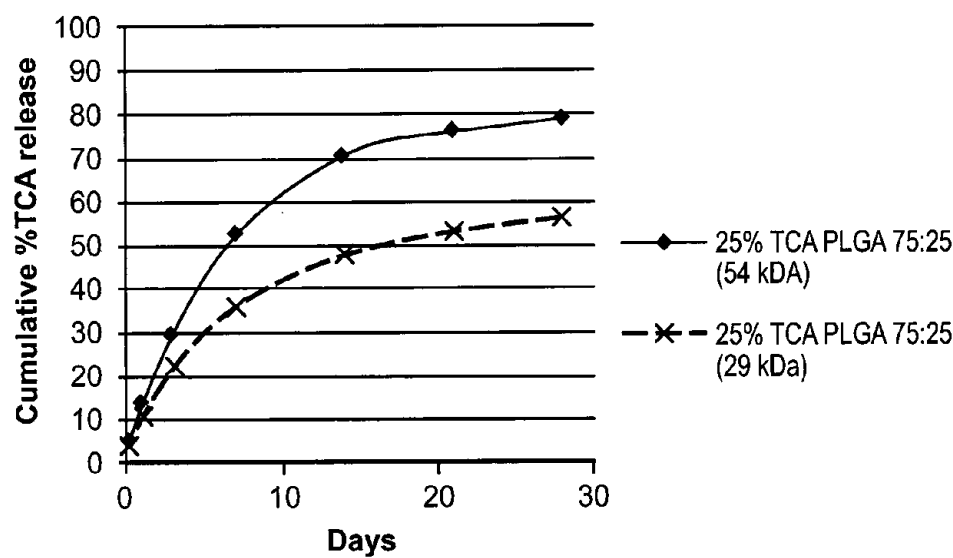


FIG. 19

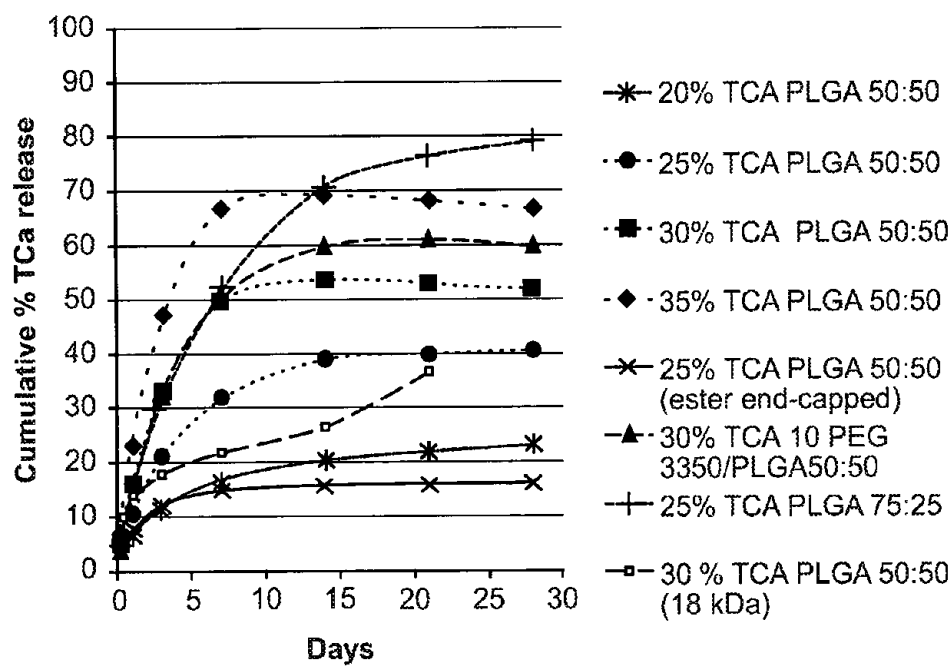


FIG. 20

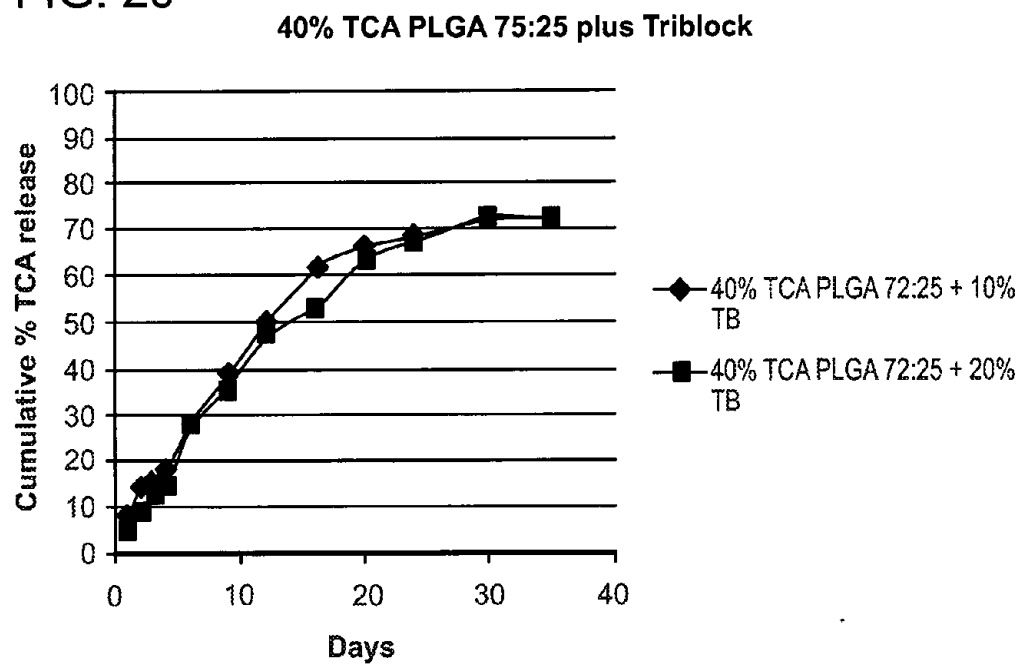


FIG. 21

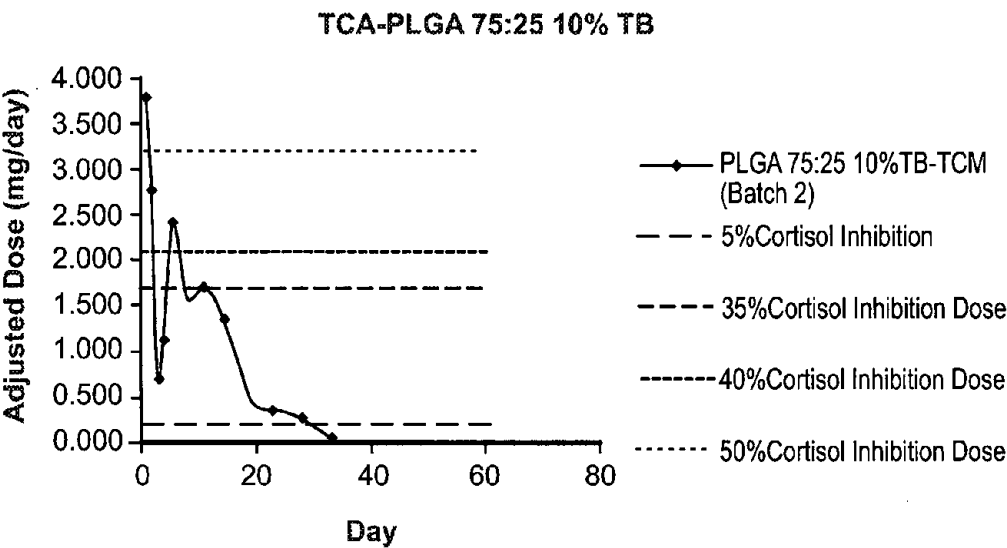


FIG. 22

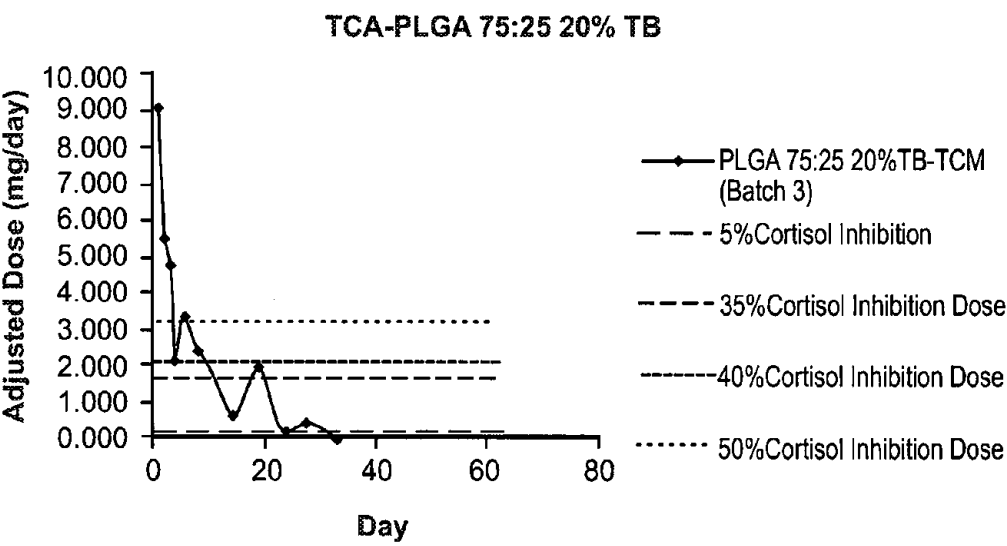


FIG. 23

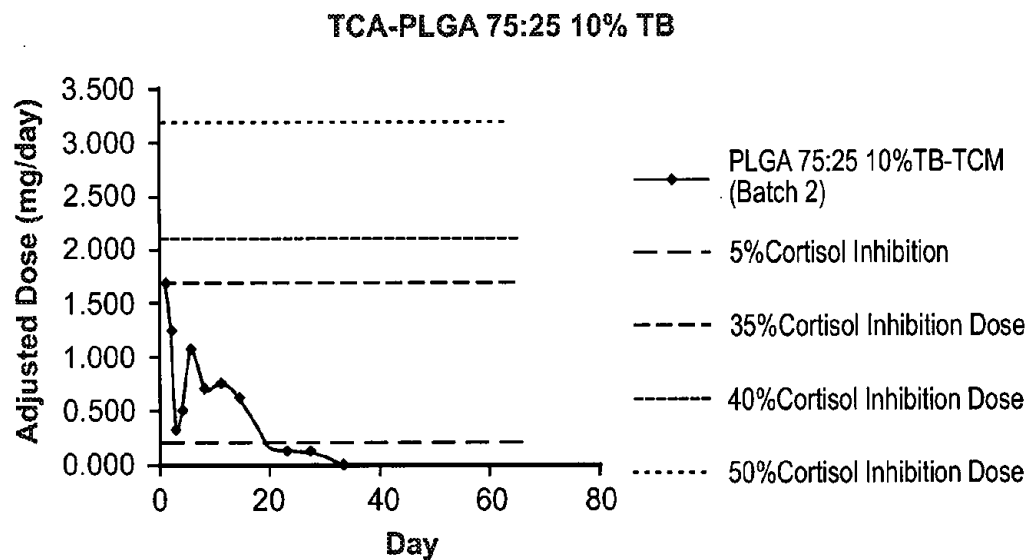


FIG. 24

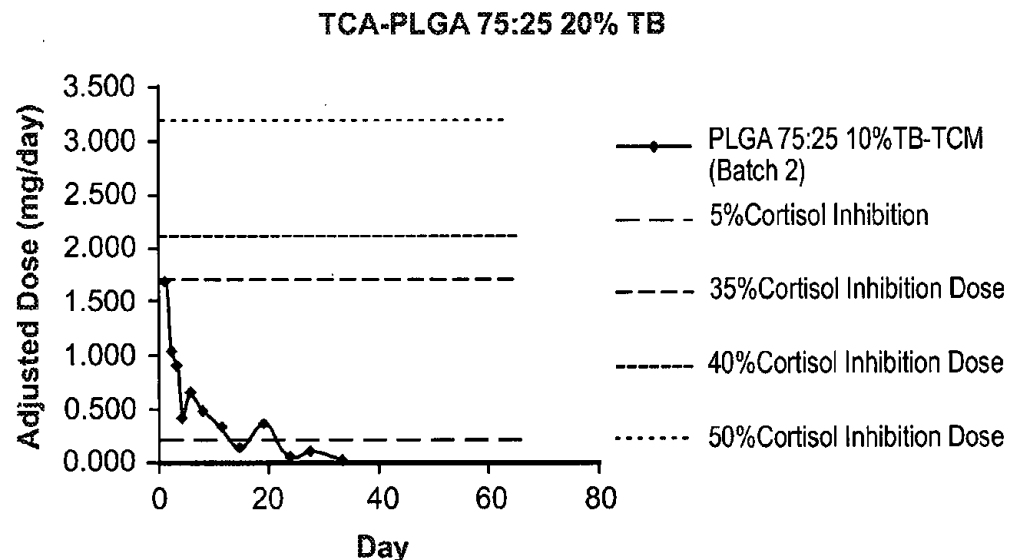


FIG. 25

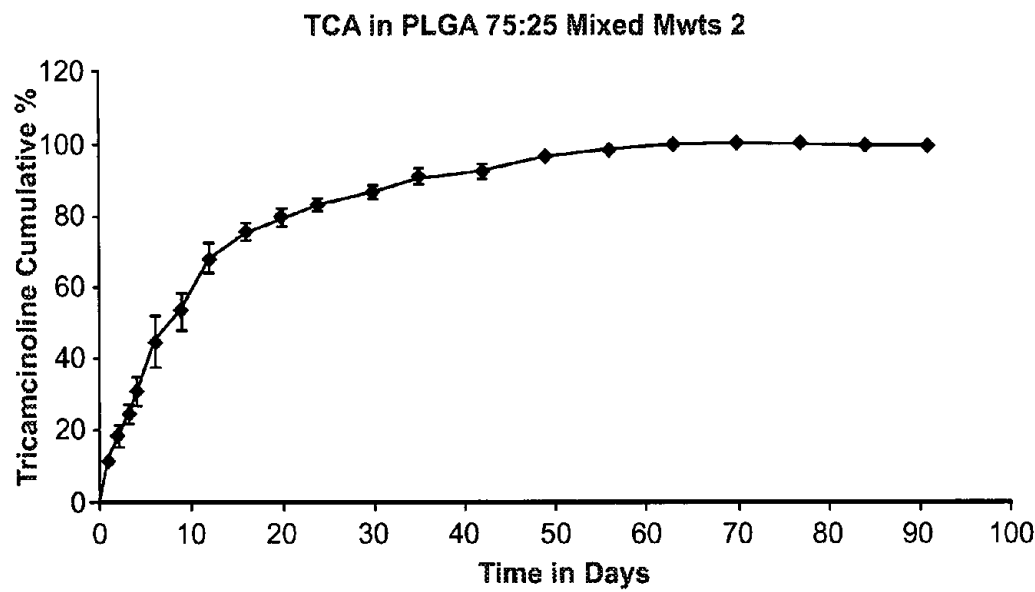


FIG. 26

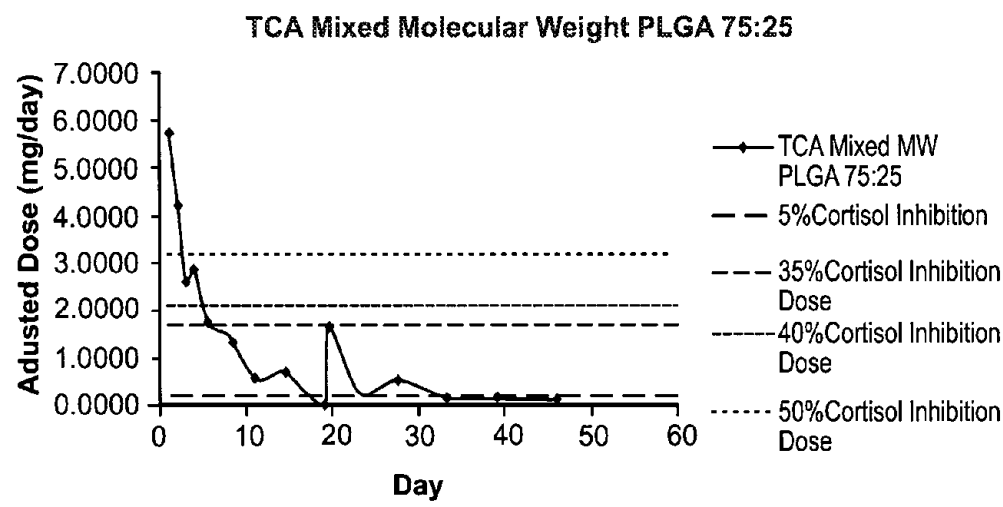


FIG. 27

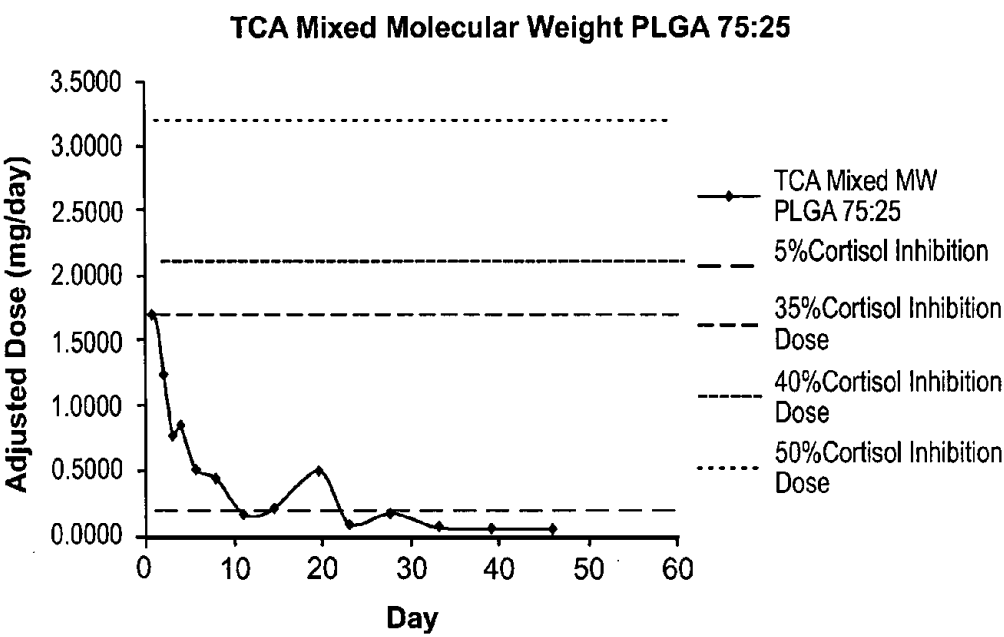


FIG. 28

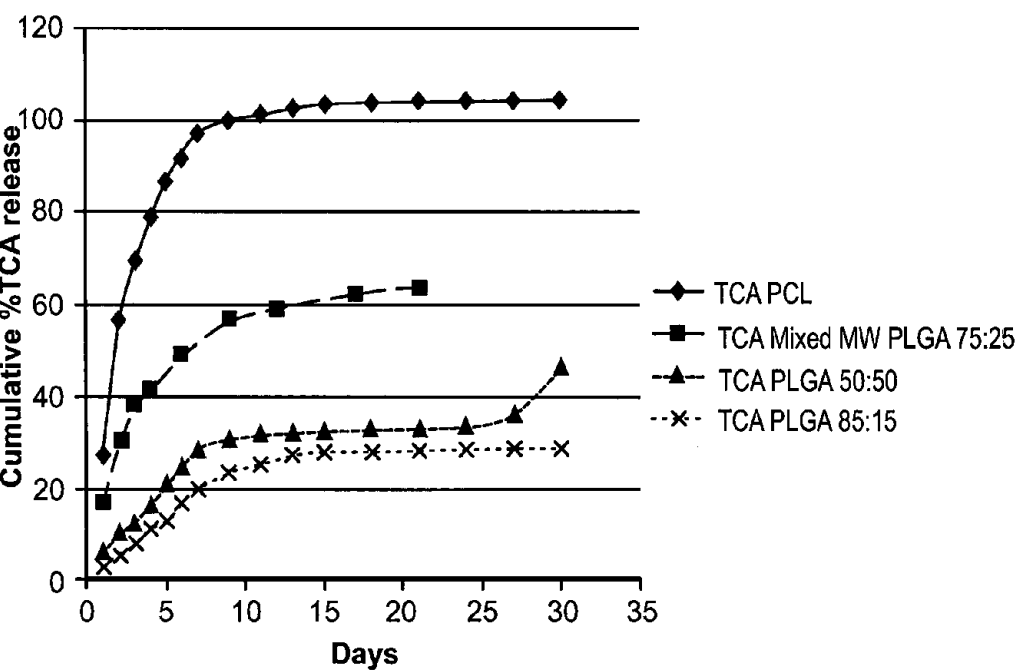


FIG. 29

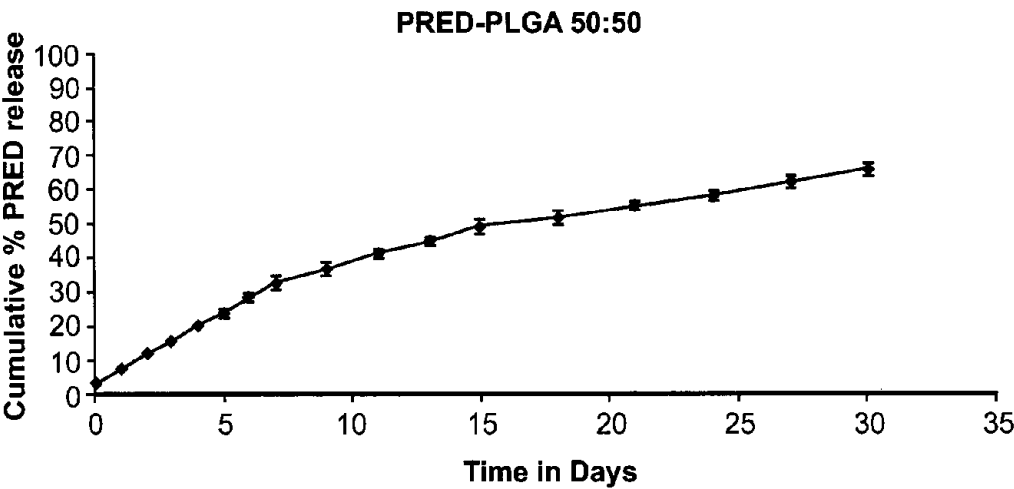


FIG. 30

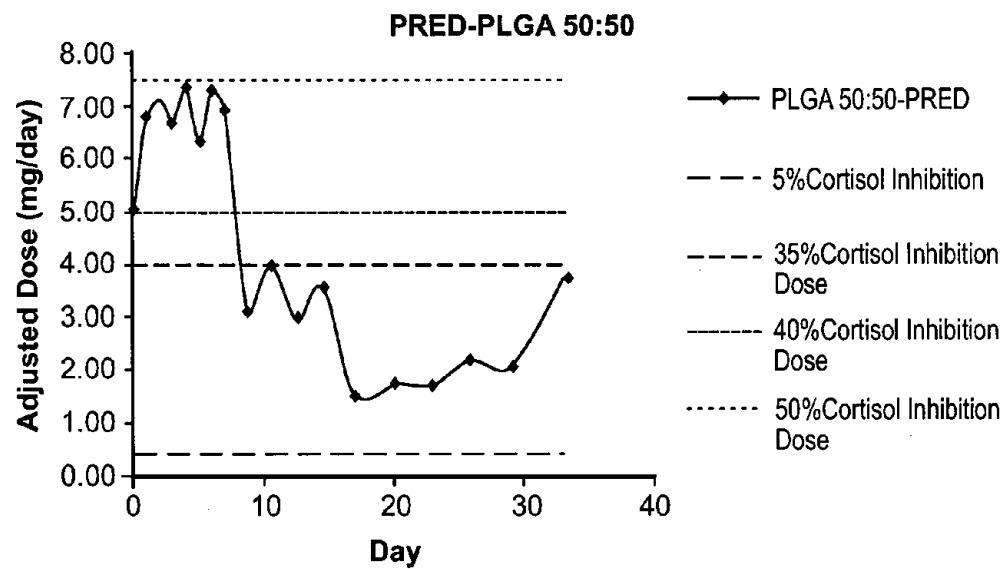


FIG. 31

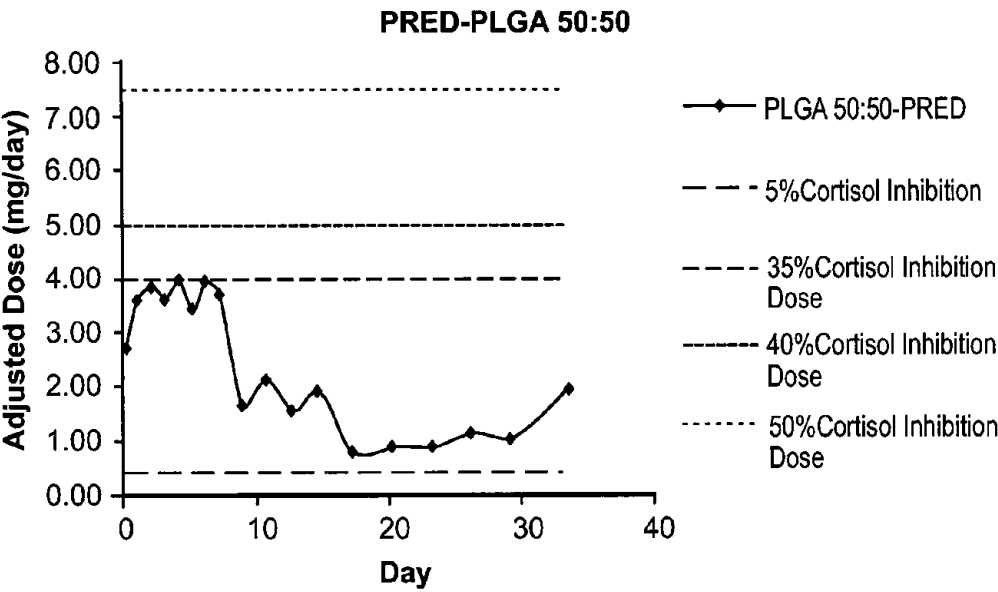


FIG. 32

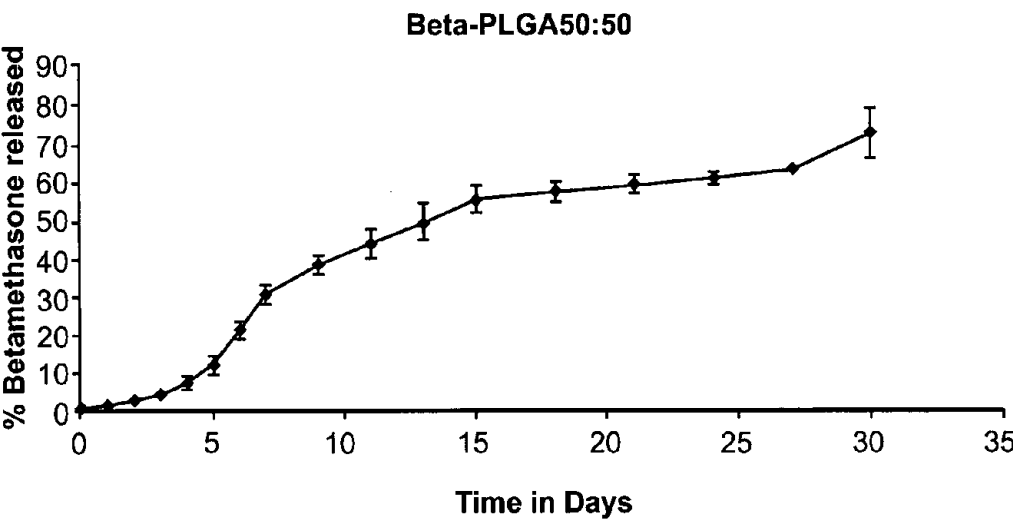


FIG. 33

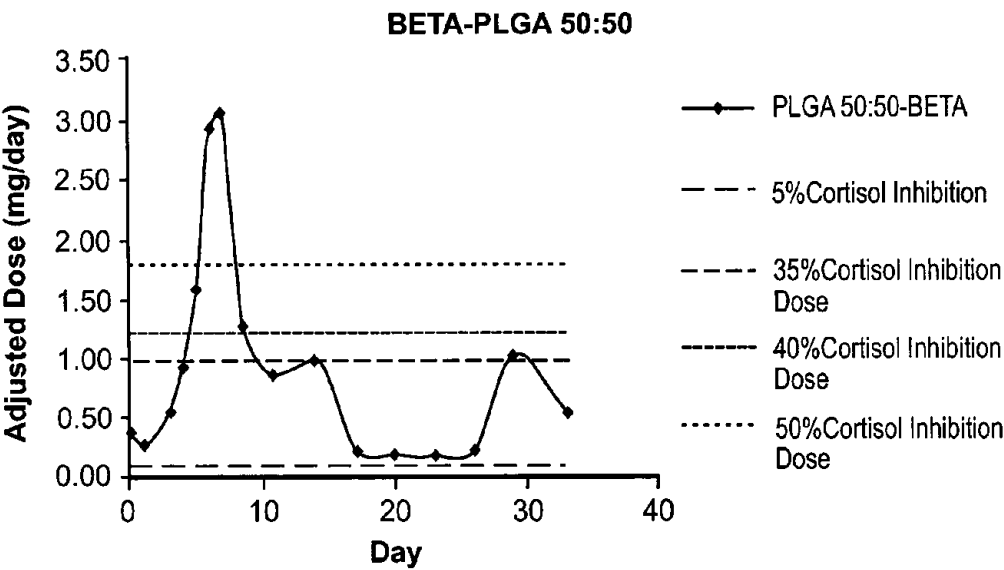


FIG. 34

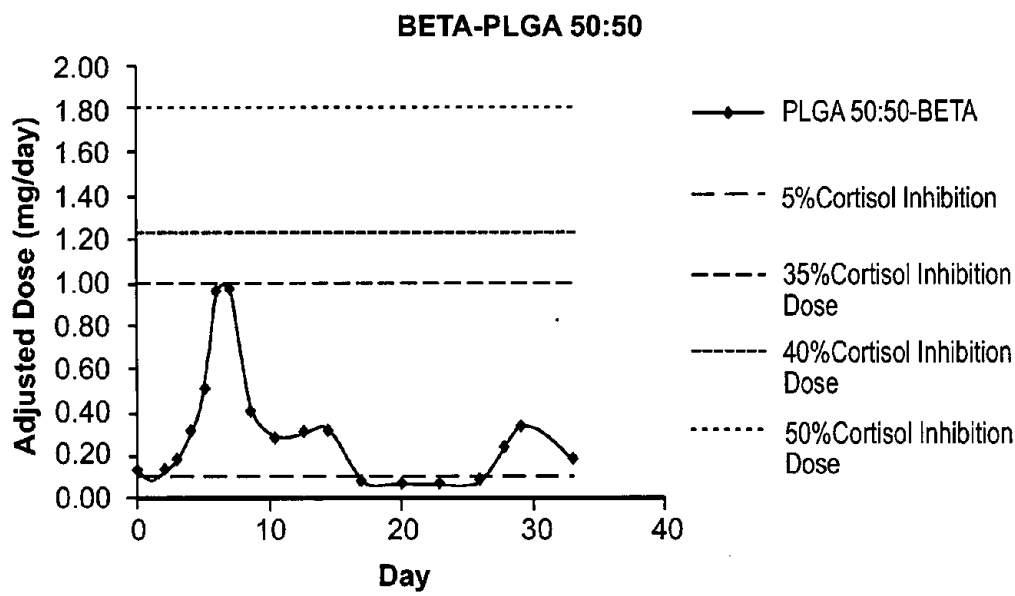


FIG. 35

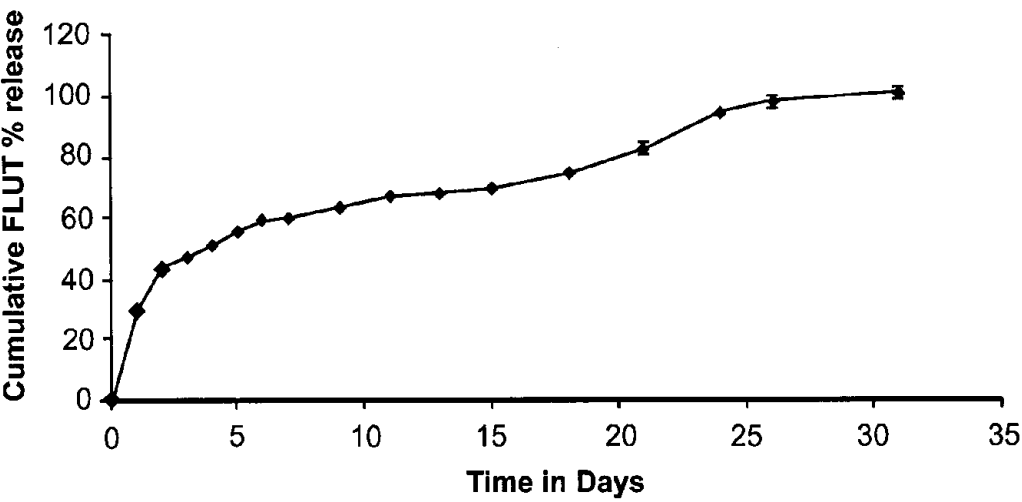


FIG. 36

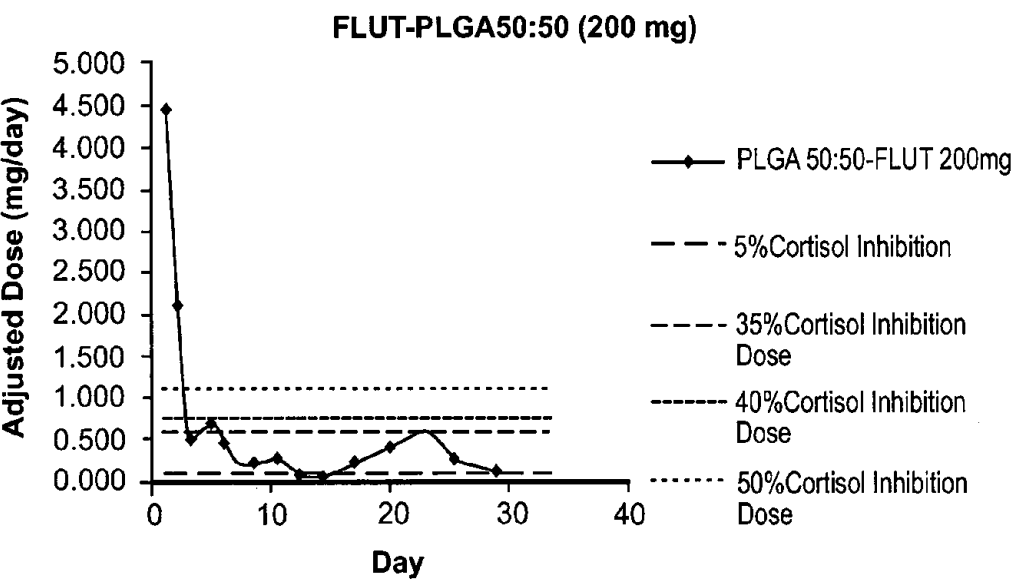


FIG. 37

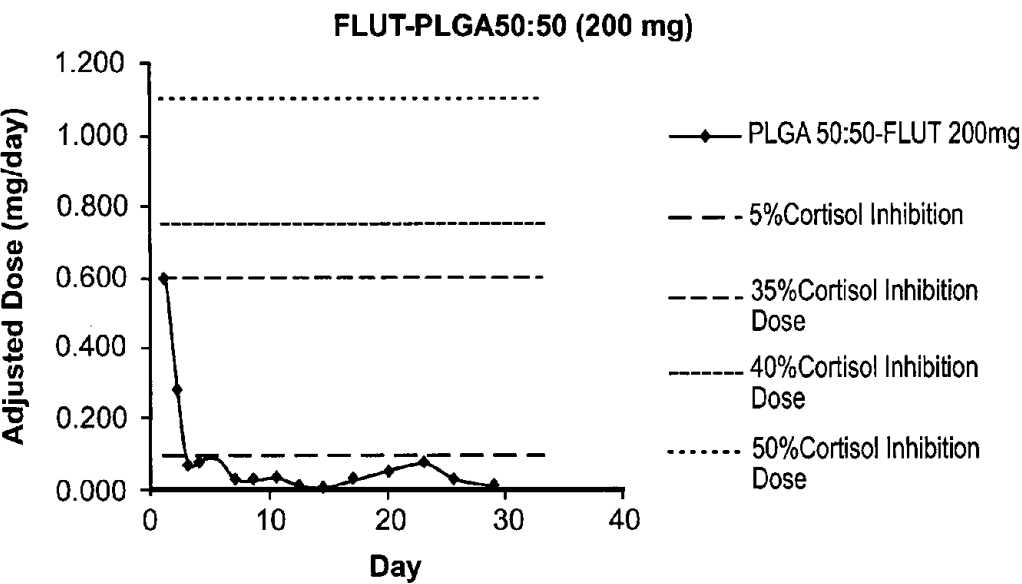
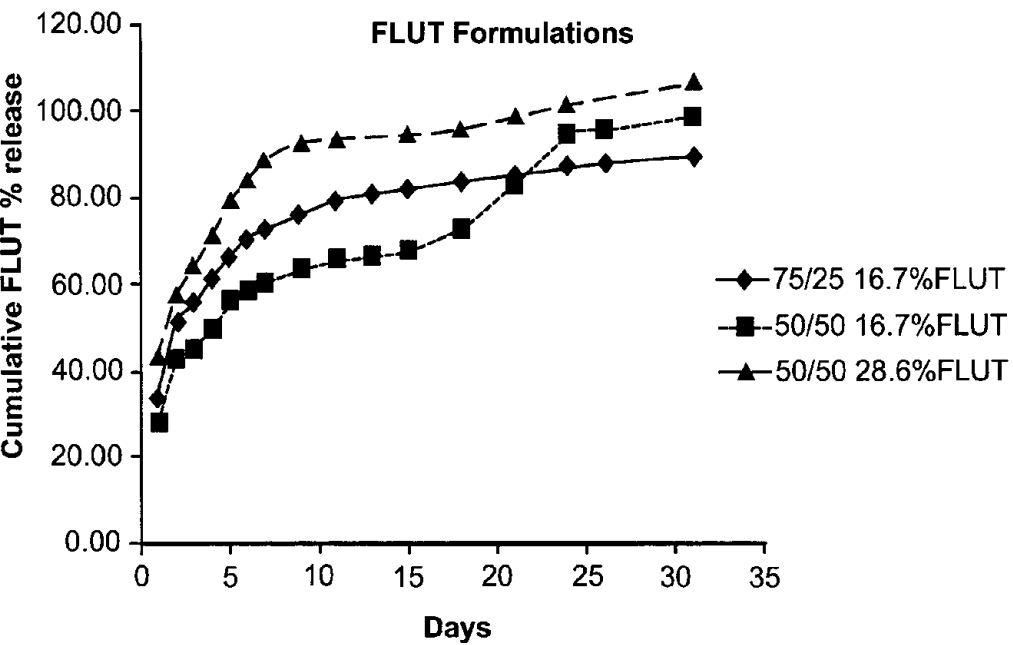


FIG. 38



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FIG. 39

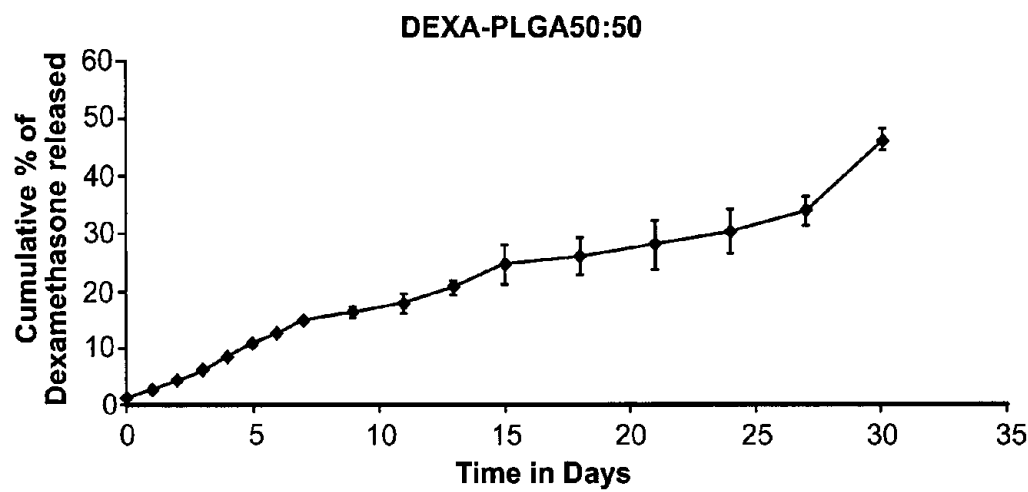


FIG. 40

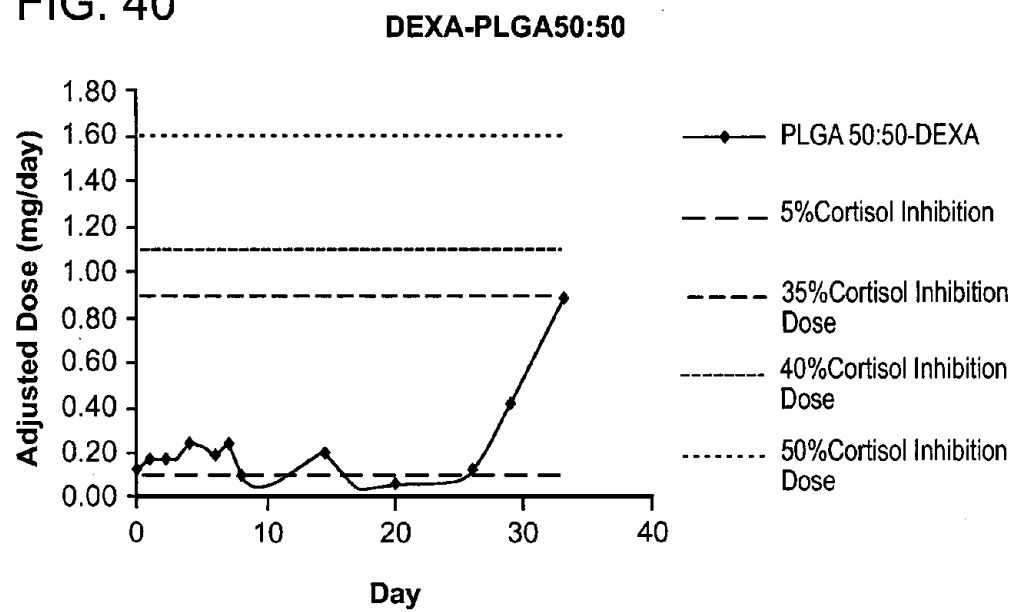


FIG. 41A

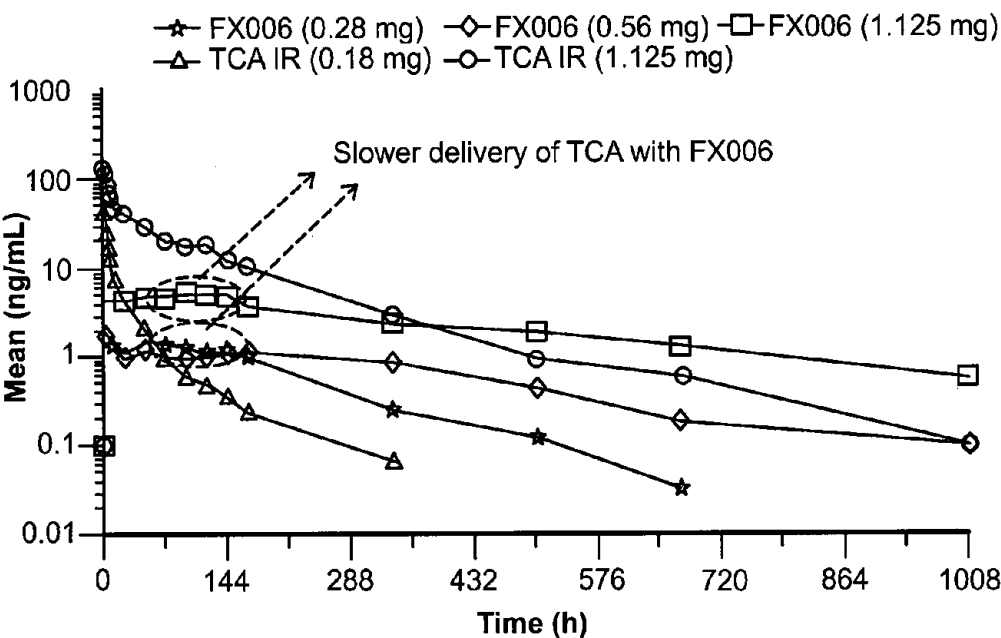


FIG. 41B

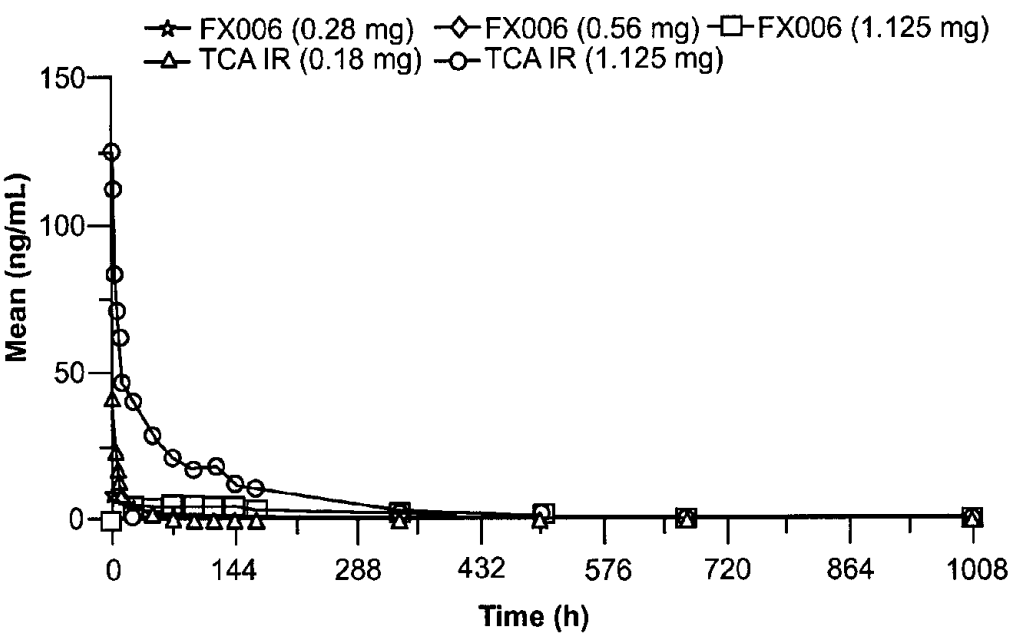


FIG. 41C

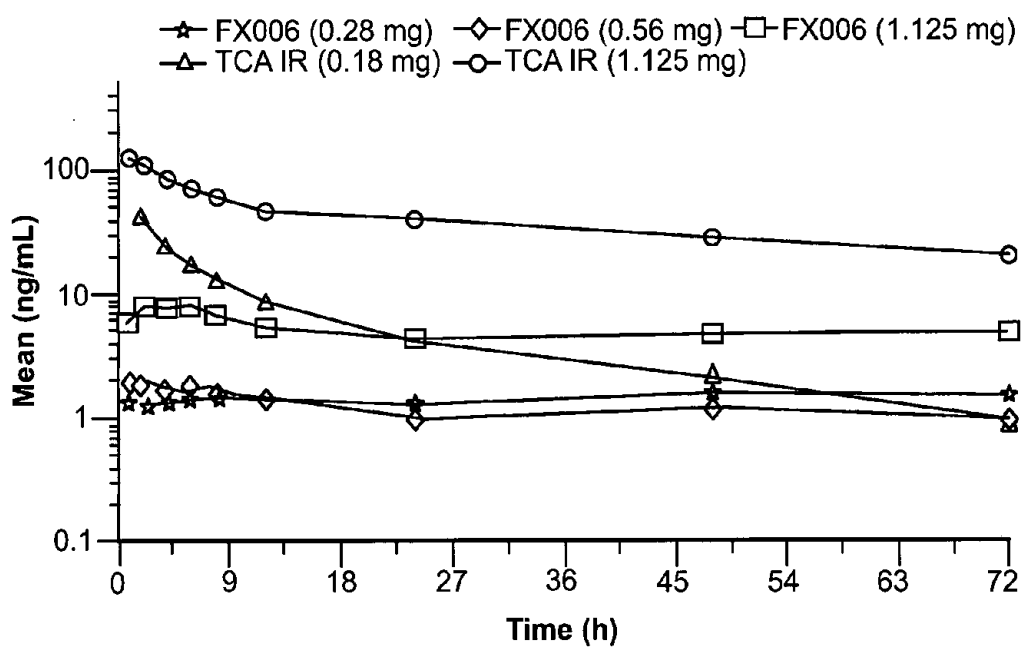


FIG. 41D

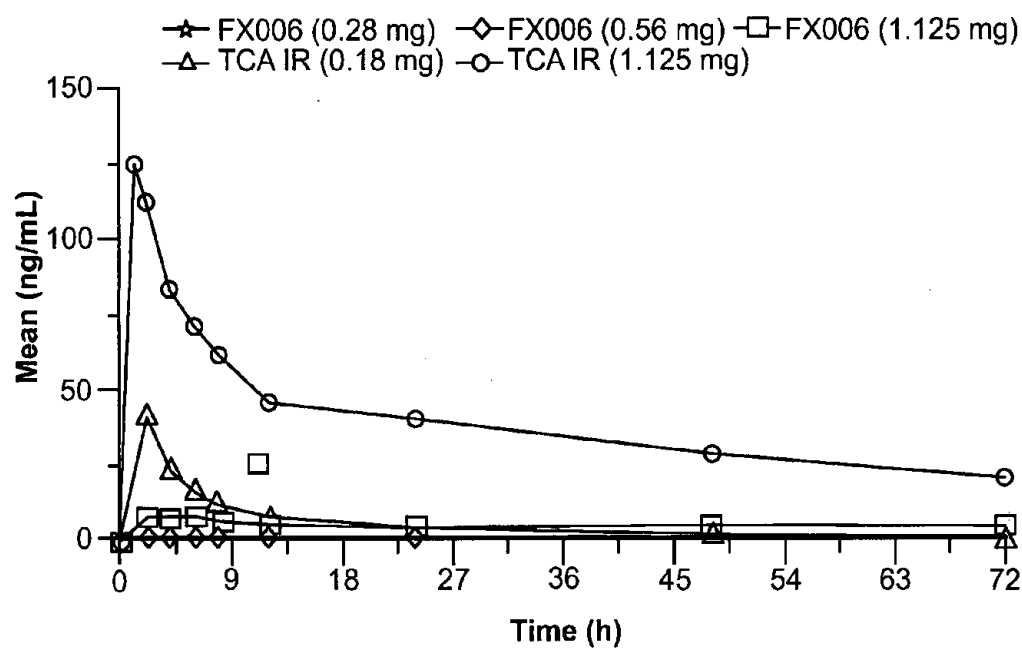


FIG. 42

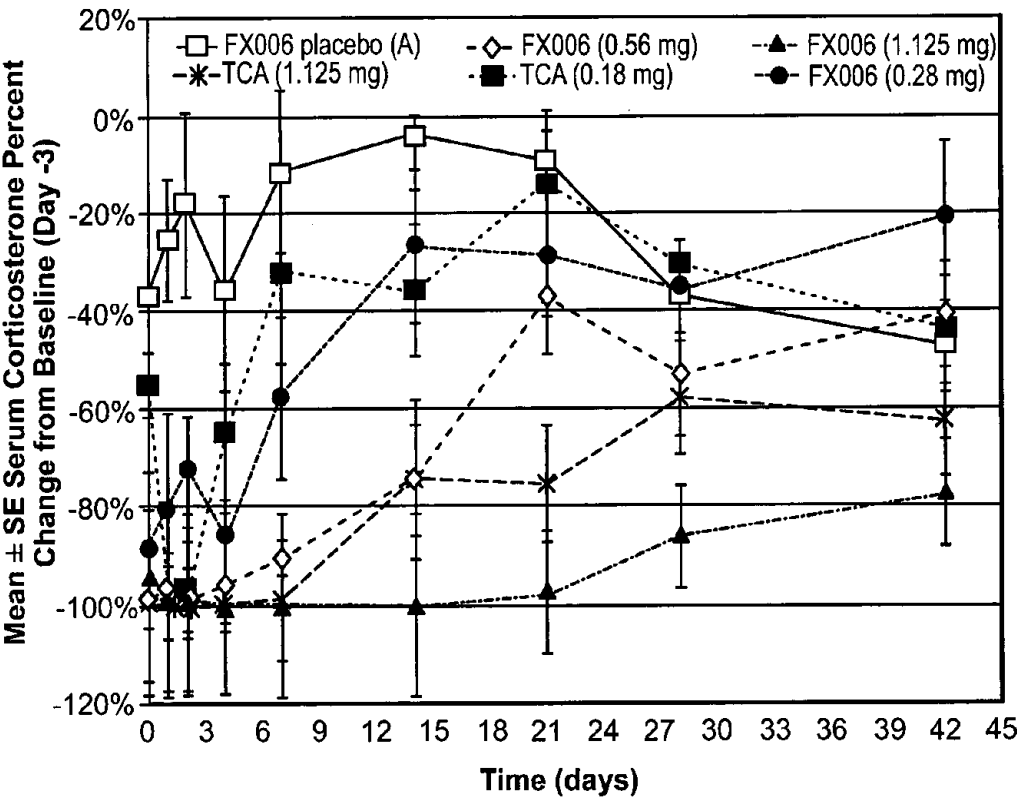


FIG. 43

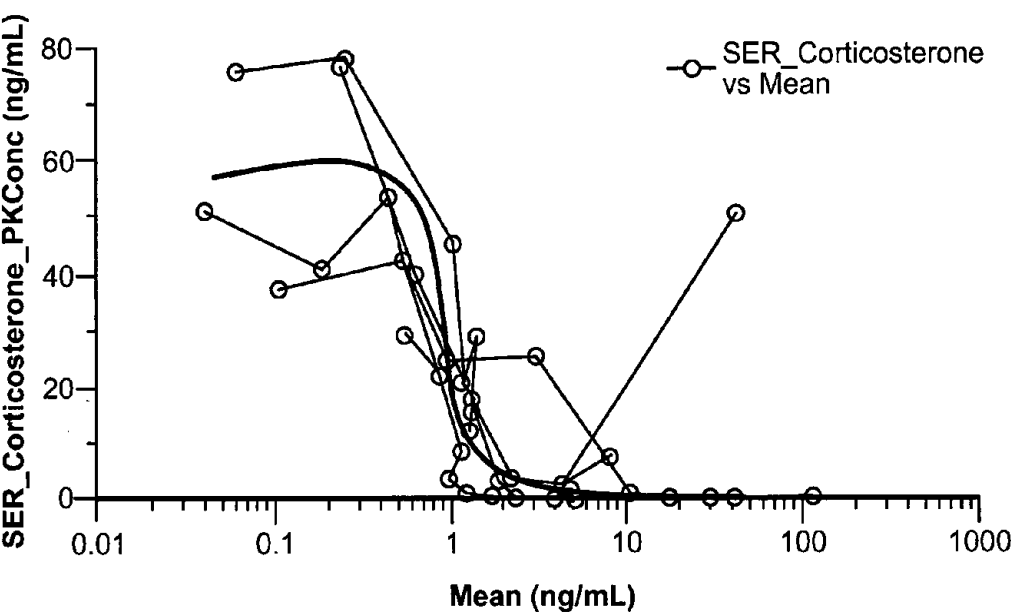


FIG. 44A

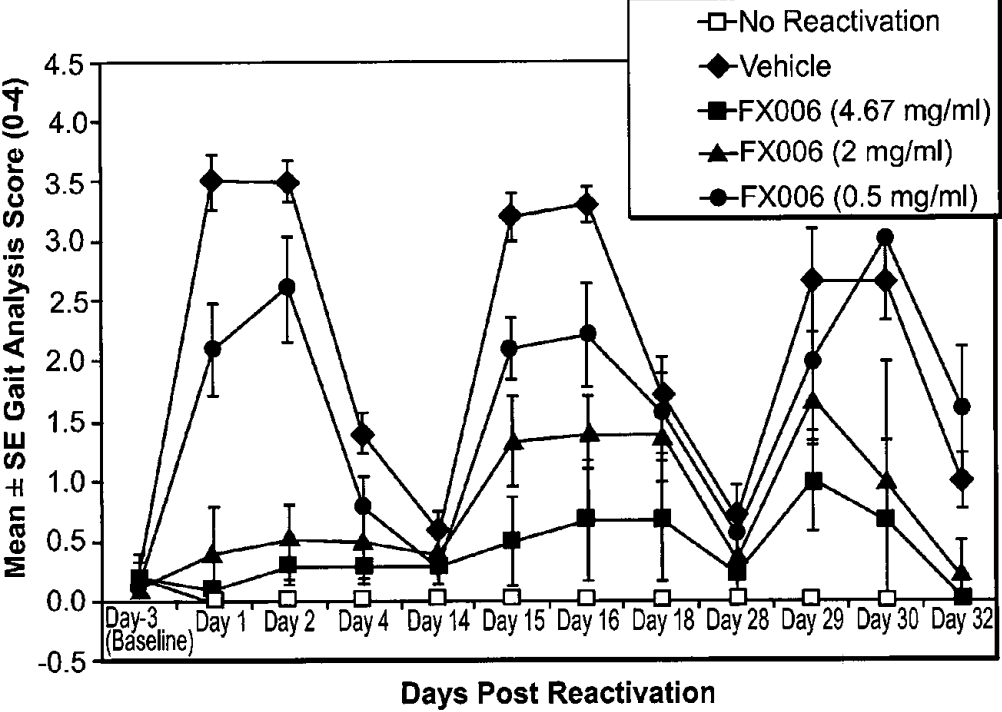
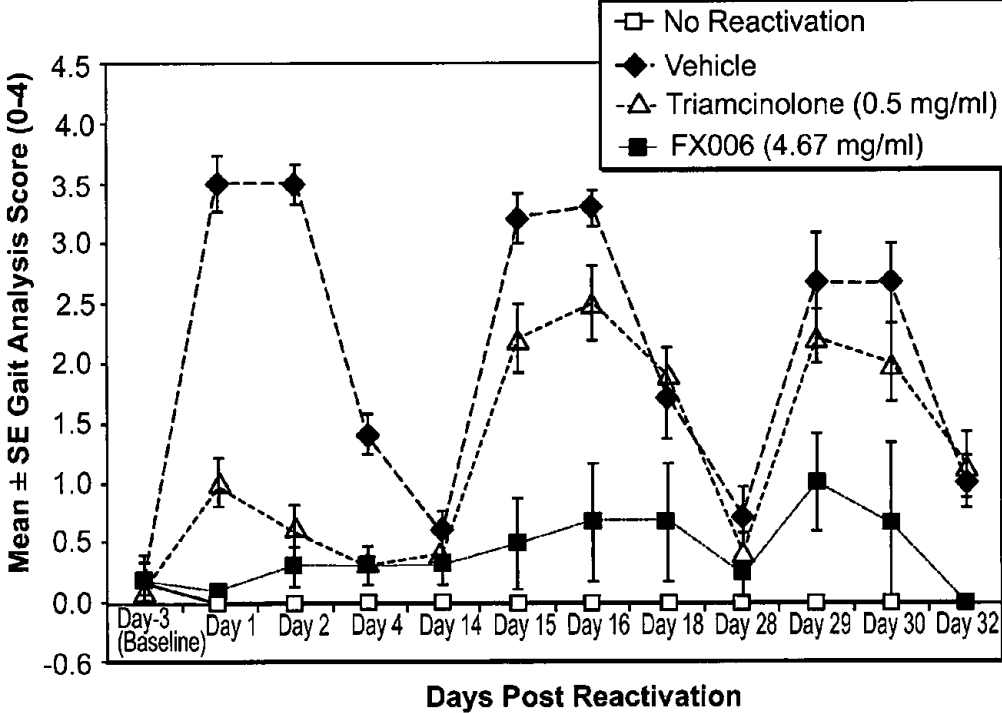


FIG. 44B



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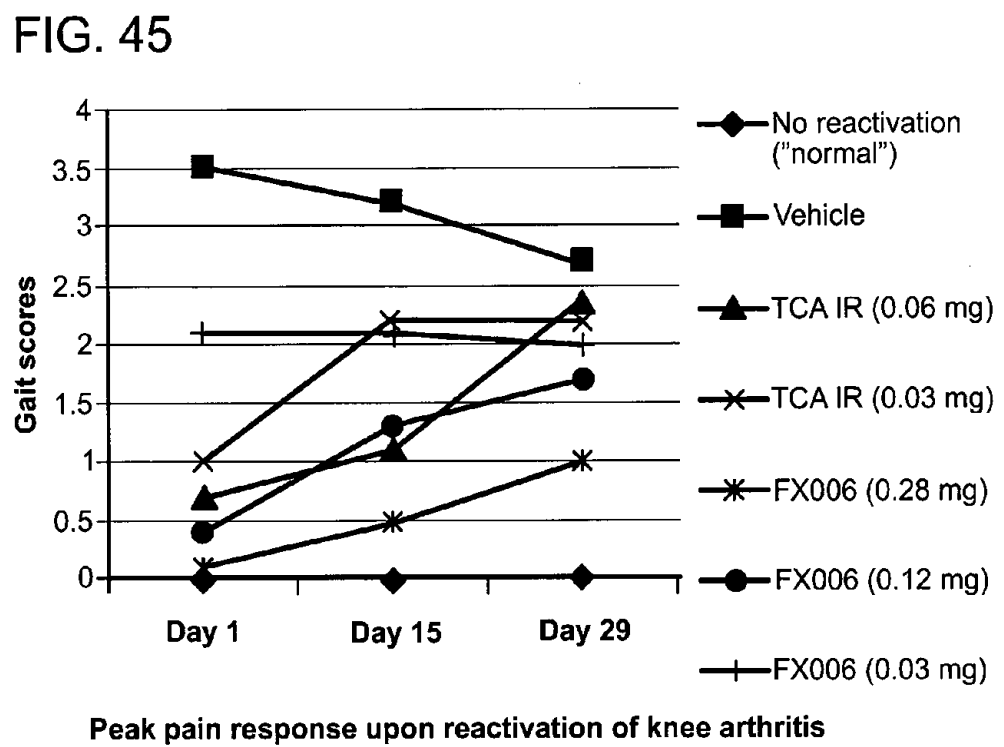
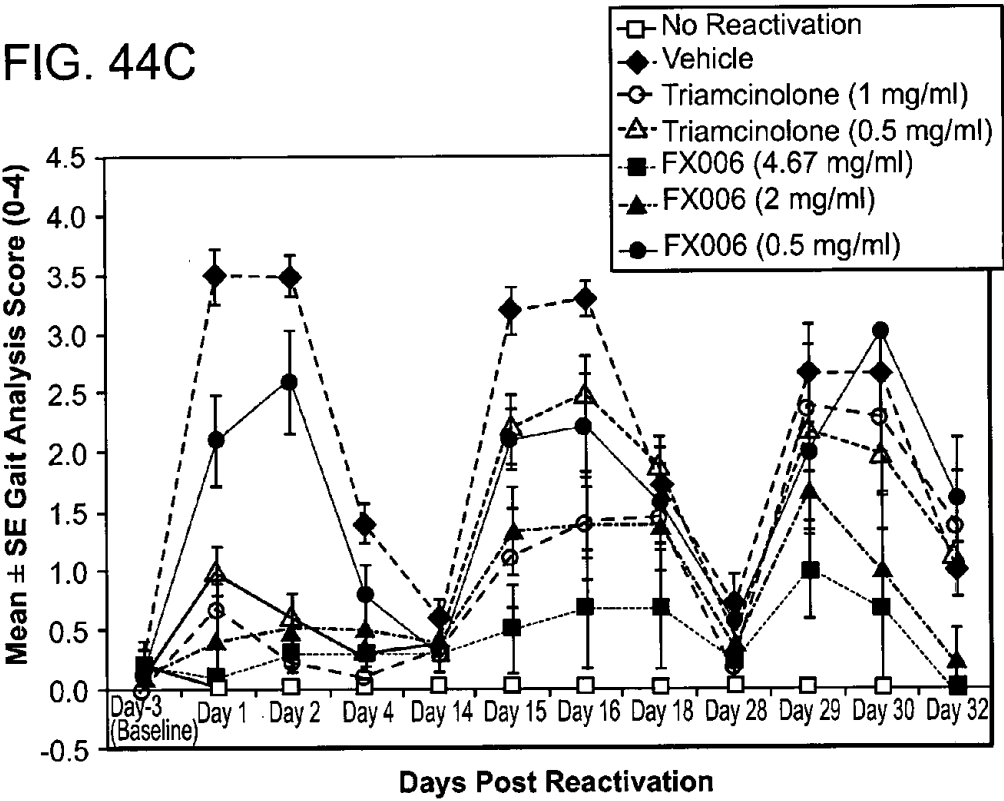


FIG. 46

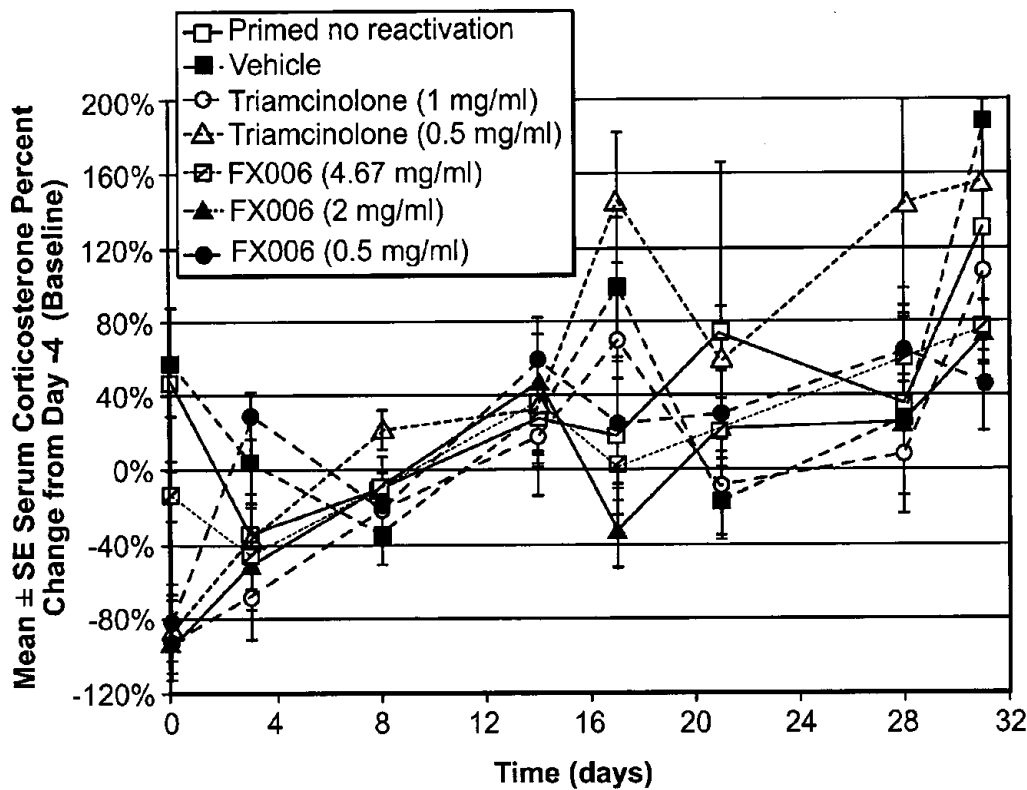


FIG. 47A

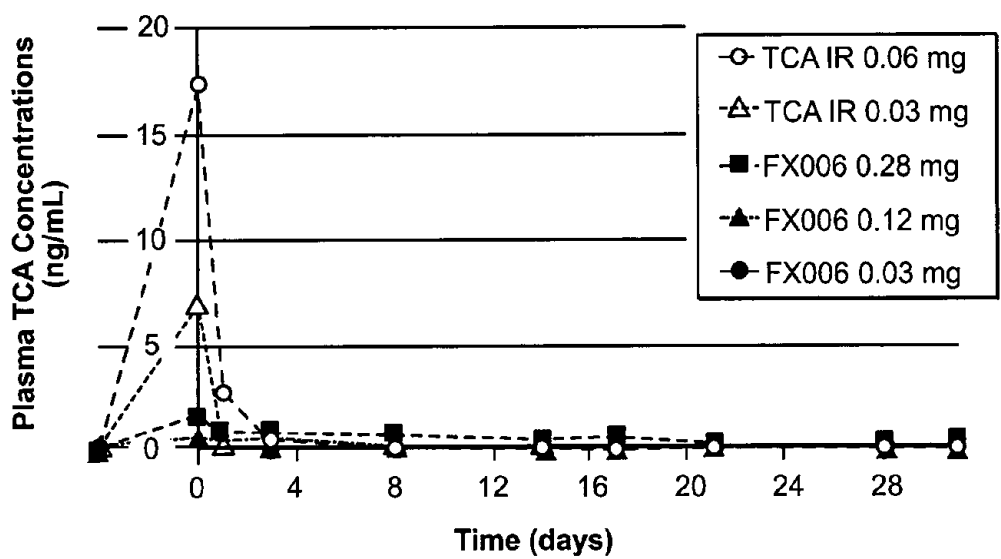


FIG. 47B

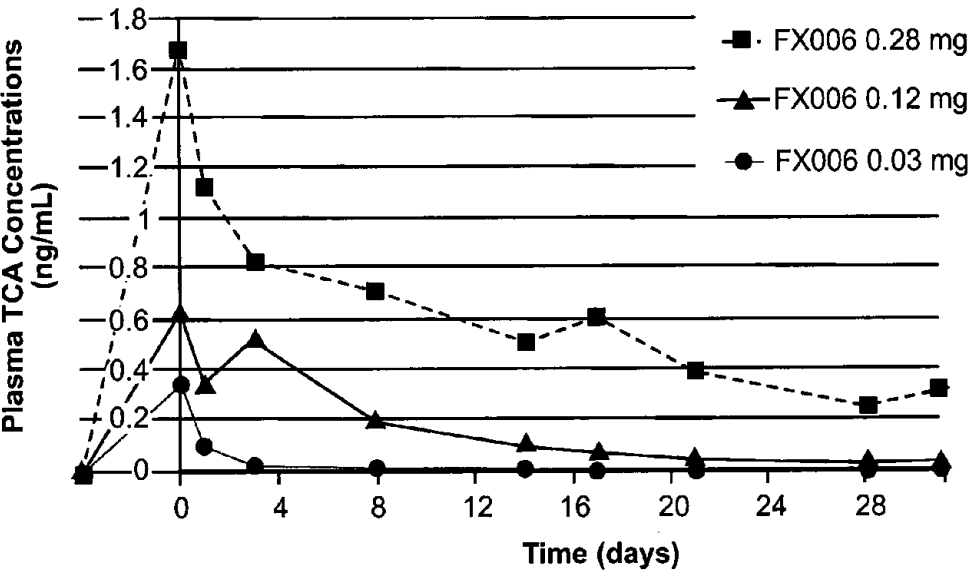
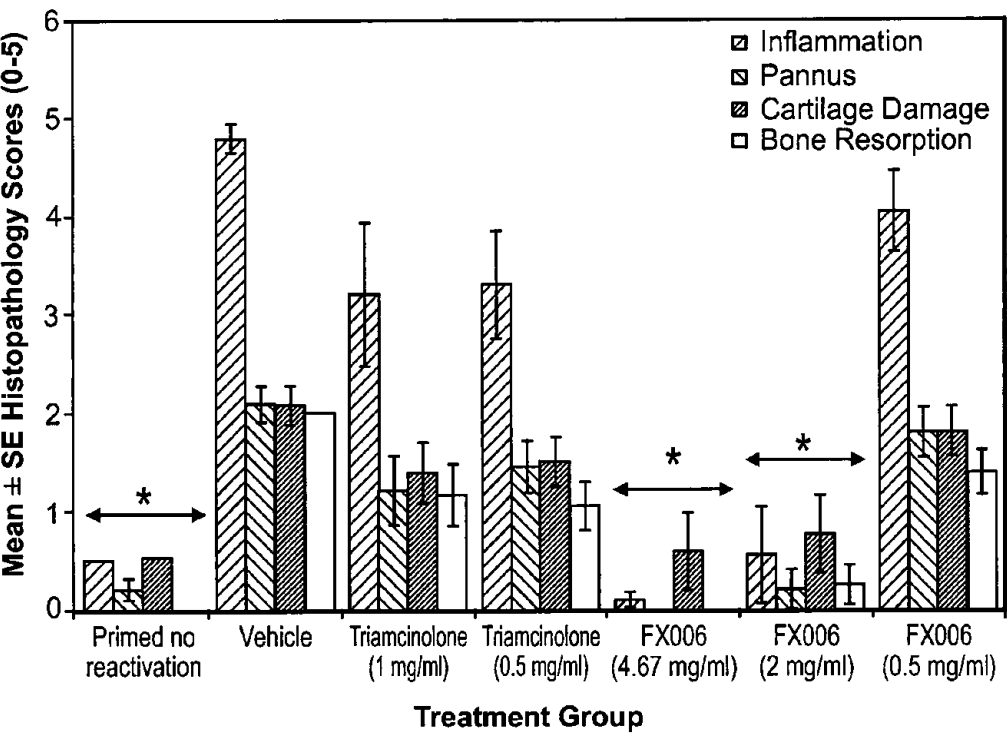


FIG. 48



**CORTICOSTEROIDS FOR THE TREATMENT
OF JOINT PAIN**

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/198,168, filed Aug. 4, 2011 claims the benefit of U.S. Provisional Application No. 61/370,666, filed Aug. 4, 2010. The contents of this application are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to the use of corticosteroids to treat pain, including pain caused by inflammatory diseases such as osteoarthritis or rheumatoid arthritis, and to slow, arrest or reverse structural damage to tissues caused by an inflammatory disease, for example damage to articular and/or peri-articular tissues caused by osteoarthritis or rheumatoid arthritis. More specifically, a corticosteroid is administered locally as a sustained release dosage form (with or without an immediate release component) that results in efficacy accompanied by clinically insignificant or no measurable effect on endogenous cortisol production.

BACKGROUND OF THE INVENTION

Corticosteroids influence all tissues of the body and produce various cellular effects. These steroids regulate carbohydrate, lipid, protein biosynthesis and metabolism, and water and electrolyte balance. Corticosteroids influencing cellular biosynthesis or metabolism are referred to as glucocorticoids while those affecting water and electrolyte balance are mineralocorticoids. Both glucocorticoids and mineralocorticoids are released from the cortex of the adrenal gland.

The administration of corticosteroids, particularly for extended periods of time, can have a number of unwanted side effects. The interdependent feedback mechanism between the hypothalamus, which is responsible for secretion of corticotrophin-releasing factor, the pituitary gland, which is responsible for secretion of adrenocorticotropic hormone, and the adrenal cortex, which secretes cortisol, is termed the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis may be suppressed by the administration of corticosteroids, leading to a variety of unwanted side effects.

Accordingly, there is a medical need to extend the local duration of action of corticosteroids, while reducing the systemic side effects associated with that administration. Thus, there is a need in the art for methods and compositions for the sustained local treatment of pain and inflammation, such as joint pain, with corticosteroids that results in clinically insignificant or no measurable HPA axis suppression. In addition, there is a medical need to slow, arrest, reverse or otherwise inhibit structural damage to tissues caused by inflammatory diseases such as damage to articular tissues resulting from osteoarthritis or rheumatoid arthritis.

SUMMARY OF THE INVENTION

Described herein are compositions and methods for the treatment of pain and inflammation using corticosteroids. The compositions and methods provided herein use one or more corticosteroids in a microparticle formulation. The corticosteroid microparticle formulations provided herein are effective at treating pain and/or inflammation with minimal long-term side effects of corticosteroid administration, including for example, prolonged suppression of the HPA axis. The

corticosteroid microparticle formulations are suitable for administration, for example, local administration by injection into a site at or near the site of a patient's pain and/or inflammation. The corticosteroid microparticle formulations provided herein are effective in slowing, arresting, reversing or otherwise inhibiting structural damage to tissues associated with progressive disease with minimal long-term side effects of corticosteroid administration, including for example, prolonged suppression of the HPA axis. The corticosteroid microparticle formulations are suitable for administration, for example, local administration by injection into a site at or near the site of structural tissue damage. As used herein, "prolonged" suppression of the HPA axis refers to levels of cortisol suppression greater than 35% by day 14 post-administration, for example post-injection. The corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-injection. In some embodiments, the corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration, for example post-injection. In some embodiments, the corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are negligible at any time post-injection. Thus, the corticosteroid microparticle formulations in these embodiments are effective in the absence of any significant HPA axis suppression. Administration of the corticosteroid microparticle formulations provided herein can result in an initial "burst" of HPA axis suppression, for example, within the first few days, within the first two days and/or within the first 24 hours post-injection, but by day 14 post-injection, suppression of the HPA axis is less than 35%.

In certain embodiments, a sustained release form of corticosteroids is administered locally to treat pain and inflammation. Local administration of a corticosteroid microparticle formulation can occur, for example, by injection into the intra-articular space, peri-articular space, soft tissues, lesions, epidural space, perineural space, or the foramenal space at or near the site of a patient's pain. In certain embodiments, the formulation additionally contains an immediate release component. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space for the treatment of pain, for example, due to osteoarthritis, rheumatoid arthritis, gouty arthritis, bursitis, tenosynovitis, epicondylitis, synovitis or other joint disorder. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into soft tissues or lesions for the treatment of inflammatory disorders, for example, the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses such as psoriasis. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an epidural space, a perineural space, a foramenal space or other spinal space for the treatment of corticosteroid-responsive degenerative musculoskeletal disorders such as Neurogenic Claudication. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space or into soft tissues to slow, arrest, reverse or otherwise

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inhibit structural damage to tissues associated with progressive disease such as, for example, the damage to cartilage associated with progression of osteoarthritis.

In certain embodiments of the invention, a combination of an immediate release form and a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space for the treatment of pain, for example, due to osteoarthritis, rheumatoid arthritis or other joint disorder(s). In certain embodiments of the invention, a combination of an immediate release form and a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space or into soft tissues to slow, arrest, reverse or otherwise inhibit structural damage to tissues associated with progressive disease such as, for example, the damage to cartilage associated with progression of osteoarthritis. The formulations and methods of embodiments of the invention can achieve immediate relief of the acute symptoms (e.g., pain and inflammation) of these diseases or conditions and additionally provide a sustained or long term therapy (e.g., slowing, arresting, reversing or otherwise inhibiting structural damage to tissues associated with progressive disease), while avoiding long term systemic side effects associated with corticosteroid administration, including HPA suppression.

In one aspect, a formulation is provided wherein a microparticle matrix (such as PLGA, PLA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the corticosteroid microparticle formulation provides at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days of a sustained, steady state release of the corticosteroid. In one aspect, a formulation is provided wherein a microparticle matrix (such as PLGA, PLA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the corticosteroid microparticle formulation provides at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days of a sustained, steady state release of the corticosteroid at a rate that does not adversely suppress the HPA axis.

The corticosteroid microparticle formulation retains sustained efficacy even after the corticosteroid is no longer resident at the site of administration, for example, in the intra-articular space, and/or after the corticosteroid is no longer detected in the systemic circulation. The corticosteroid microparticle formulation retains sustained efficacy even after the corticosteroid microparticle formulation is no longer resident at the site of administration, for example, in the intra-articular space, and/or the corticosteroid microparticle formulation is no longer detected in the systemic circulation. The corticosteroid microparticle formulation retains sustained efficacy even after the corticosteroid microparticle formulation ceases to release therapeutically effective amounts of corticosteroid. For example, in some embodiments, the corticosteroid released by the microparticle formulation retains efficacy for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least six weeks, at least seven weeks, at least eight weeks, at least nine weeks, at least twelve weeks, or more than twelve-weeks post-administration. In some embodiments, the corticosteroid released by the microparticle formulation retains efficacy for a time period that is at least twice as long, at least three times as long, or more than three times as long as the residency period for the corticosteroid and/or the corticosteroid microparticle formulation. In some embodiments, the sustained, steady state release of corticosteroid will not adversely suppress the HPA axis.

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In some embodiments, a controlled or sustained-release formulation is provided wherein a microparticle matrix (such as PLGA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the formulation may or may not exhibit an initial rapid release, also referred to herein as an initial "burst" of the corticosteroid for a first length of time of between 0 and 14 days, for example, between the beginning of day 1 through the end of day 14, in addition to the sustained, steady state release of the corticosteroid for a second length of time of at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days. It should be noted that when corticosteroid levels are measured in vitro, an occasional initial burst of corticosteroid release from the microparticle formulation can be seen, but this initial burst may or may not be seen in vivo. In another embodiment, a controlled or sustained-release formulation is provided wherein a microparticle matrix (such as PLGA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the formulation may or may not exhibit an initial rapid release, also referred to herein as an initial "burst" of the corticosteroid for a first length of time of between 0 and 14 days, e.g., between the beginning of day 1 through the end of day 14, in addition to the sustained, steady state release of the corticosteroid for a second length of time of at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days where the sustained, steady state release of corticosteroid is released at a rate that does not suppress the HPA axis at a level greater than 50% at day 14 post-administration. In some embodiments, the sustained, steady state release of corticosteroid will not adversely suppress the HPA axis, for example, the level of HPA axis suppression at or less than 35% by day 14 post-administration. In some embodiments, the sustained, steady state release of corticosteroid does not significantly suppress the HPA axis, for example, the level of HPA axis suppression is negligible and/or undetectable by day 14 post-injection. In some embodiments, the sustained, steady state release of corticosteroid does not significantly suppress the HPA axis, for example, the level of HPA axis suppression is negligible at all times post-injection. In some embodiments, the length of sustained release is between 21 days and 90 days. In some embodiments, the length of sustained release is between 21 days and 60 days. In some embodiments, the length of sustained release is between 14 days and 30 days. In some embodiments, the length of release of the initial "burst" component is between 0 and 10 days, for example between the beginning of day 1 through the end of day 10. In some embodiments, the length of release of the initial "burst" component is between 0 and 6 days, for example between the beginning of day 1 through the end of day 6. In some embodiments, the length of initial "burst," component is between 0 and 2 days, for example between the beginning of day 1 through the end of day 2. In some embodiments, the length of initial "burst" component is between 0 and 1 day, for example between the beginning of day 1 through the end of day 1.

The corticosteroid microparticle formulations provided herein can be used in combination with any of a variety of therapeutics, also referred to herein as "co-therapies." For example, the corticosteroid microparticle formulations can be used in combination with an immediate release corticosteroid solution or suspension, which provides high local exposures for between 1 day and 14 days following administration and which produce systemic exposures that may be associated with transient suppression of the HPA axis. For example, 40 mg of immediate release triamcinolone acetate co-administered with the corticosteroid microparticle formulation in the intra-articular space would be

expected to produce high local concentrations lasting for about 12 days. These high local concentrations would be associated with peak plasma concentration of triamcinolone acetonide of approximately 10 ng/ml on day 1, and over the course of the first 12 days of release of the triamcinolone acetonide from the intra-articular space would be associated with transient suppression of the HPA axis with a maximal effect of approximately 60% suppression of cortisol on day 1-2 (Derendorf et al., "Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration." *Clin Pharmacol Ther.* 39(3) (1986):313-7). By day 12, the contribution of the immediate release component to the plasma concentration would be small, less than 0.1 ng/ml, and the contribution to the intra articular concentration of the immediate release component would also be small. However at day 12 and beyond, the corticosteroid microparticle formulation would continue to release corticosteroid in the intra articular space at a rate that extends the duration of therapeutic effect and does not suppress the HPA axis. In some embodiments, the same corticosteroid is used in both the immediate release and sustained release components. In some embodiments, the immediate release component contains a corticosteroid that is different from that of the sustained, steady state release of corticosteroid will not adversely suppress the HPA axis. In some embodiments, the period of sustained release is between 21 days and 90 days. In some embodiments, the period of sustained release is between 21 days and 60 days. In some embodiments, the period of sustained release is between 14 days and 30 days. In some embodiments, the high local exposure attributable to the immediate release component lasts for between 1 day and 14 days. In some embodiments, the high local exposure attributable to the immediate release component lasts for between 1 day and 10 days. In some embodiments, the high local exposure attributable to the immediate release component lasts between 1 days and 8 days. In some embodiments, the high local exposure attributable to the immediate release component lasts between 1 days and 6 days. In some embodiments, the high local exposure attributable to the immediate release component lasts for between 1 day and 4 days.

Upon administration, the corticosteroid microparticle formulation may provide an initial release of corticosteroid at the site of administration, for example, in the intra-articular space and/or peri-articular space. Once the initial release of corticosteroid has subsided, the controlled or sustained release of the corticosteroid microparticle formulations continues to provide therapeutic (e.g., intra-articular and/or peri-articular) concentrations of corticosteroid to suppress inflammation, maintain analgesia, and/or slow, arrest or reverse structural damage to tissues for an additional period of therapy following administration (FIG. 1, top tracings). However, the systemic exposure associated with the sustained release component does not suppress the HPA axis (FIG. 1, bottom tracings). Thus, the invention includes therapies and formulations that may exhibit an initial release of corticosteroid followed by controlled or sustained release where the therapy comprises a period of therapy wherein the corticosteroid is released from the sustained release component and the plasma levels of the corticosteroid does not adversely suppress the HPA axis.

In some embodiments, the length of sustained release is between 21 days and 90 days. In some embodiments, the length of sustained release is between 21 days and 60 days. In some embodiments, the length of sustained release is between 14 days and 30 days. In some embodiments, the length of release of the immediate release form is between 1 day and 14

days. In some embodiments, the length of release of the immediate release form is between 1 day and 10 days. In some embodiments, the length of release of the immediate release form is between 1 day and 8 days. In some embodiments, the length of release of the immediate release form is between 1 day and 6 days. In some embodiments, the length of release of the immediate release form is between 1 day and 4 days.

The invention provides populations of microparticles including a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid is between 22% to 28% of the microparticles.

The invention also provides controlled or sustained release preparation of a Class B corticosteroid that include a lactic acid-glycolic acid copolymer microparticle containing the Class B corticosteroid, wherein the Class B corticosteroid is between 22% to 28% of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention also provides formulations that include (a) controlled- or sustained-release microparticles comprising a Class B corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.3 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 80:20 to 60:40; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped.

In some embodiments of these populations, preparations and/or formulations, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid from the range of about 80:20 to 60:40. In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 75:25.

The invention also provides populations of microparticles including a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a mixed molecular weight lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid is between 12% to 28% of the microparticles. In some embodiments, the corticosteroid microparticle formulation includes a Class B corticosteroid and a microparticle made using 75:25 PLGA formulation with two PLGA polymers, one of low molecular weight and one of high molecular weight in a two to one ratio, respectively. The low molecular weight PLGA has a molecular weight of range of 15-35 kDa and an inherent viscosity range from 0.2 to 0.35 dL/g and the high molecular weight PLGA has a range of 70-95 kDa and an inherent viscosity range of 0.5 to 0.70 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 μ m, or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

The invention also provides populations of microparticles including a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid

copolymer matrix containing 10-20% triblock (PEG-PLGA-PEG) having an inherent viscosity in the range from 0.6 to 0.8 dL/g, wherein the Class B corticosteroid is between 22% to 28% of the microparticles. In some embodiments, the corticosteroid microparticle formulation includes a Class B corticosteroid and a microparticle made using 75:25 PLGA formulation and containing 10-20% triblock (PEG-PLGA-PEG) having an inherent viscosity in the range from 0.6 to 0.8 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

These Class B corticosteroid microparticle formulations, preparations, and populations thereof, when administered to a patient, exhibit reduced undesirable side effects in patient, for example, undesirable effects on a patient's cartilage or other structural tissue, as compared to the administration, for example administration into the intra-articular space of a joint, of an equivalent amount of the Class B corticosteroid absent any microparticle or other type of incorporation, admixture, or encapsulation.

In some embodiments, the Class B corticosteroid is triamcinolone acetonide or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, the total dose of corticosteroid contained in the microparticles is in the range of 10-90 mg, where the Class B corticosteroid is between 12-28% of the microparticle, for example, between 22-28% of the microparticle (i.e., when the corticosteroid is 28% of the microparticle, the microparticle is in the range of 35.7-321.4 mgs, and so on for all values between 22-28% load dose, when the corticosteroid is 25% of the microparticle, the microparticle is in the range of 40-360 mgs, when the corticosteroid is 22% of the microparticle, the microparticle is in the range of 45.5-409.1 mgs, when the corticosteroid is 12% of the microparticle, the microparticle is in the range of 83.3-750 mgs, and so on for all values between 12-28% load dose). In some embodiments, the Class B corticosteroid contained in the microparticles is 12-28% of the microparticle, for example, between 22-28% of the microparticle and the total dose of corticosteroid is in a range selected from 10-80 mg, 10-70 mg, 10-60 mg, 10-50 mg, 10-40 mg, 10-30 mg, 10-20 mg, 20-90 mg, 20-80 mg, 20-70 mg, 20-60 mg, 20-50 mg, 20-40 mg, 20-30 mg, 20-20 mg, 20-10 mg, 20-0 mg, 30-90 mg, 30-80 mg, 30-70 mg, 30-60 mg, 30-50 mg, 30-40 mg, 30-30 mg, 30-20 mg, 30-10 mg, 30-0 mg, 40-90 mg, 40-80 mg, 40-70 mg, 40-60 mg, 40-50 mg, 40-40 mg, 40-30 mg, 40-20 mg, 40-10 mg, 40-0 mg, 50-90 mg, 50-80 mg, 50-70 mg, 50-60 mg, 50-50 mg, 50-40 mg, 50-30 mg, 50-20 mg, 50-10 mg, 50-0 mg, 60-90 mg, 60-80 mg, 60-70 mg, 60-60 mg, 60-50 mg, 60-40 mg, 60-30 mg, 60-20 mg, 60-10 mg, 60-0 mg, 70-90 mg, 70-80 mg, 70-70 mg, 70-60 mg, 70-50 mg, 70-40 mg, 70-30 mg, 70-20 mg, 70-10 mg, 70-0 mg, 80-90 mg, 80-80 mg, 80-70 mg, 80-60 mg, 80-50 mg, 80-40 mg, 80-30 mg, 80-20 mg, 80-10 mg, 80-0 mg. In some embodiments, the Class B corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μ m to 100 μ m, for example, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or

formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes triamcinolone acetonide (TCA) and a microparticle made using 75:25 PLGA formulation having an inherent viscosity in the range from 0.3 to 0.5 dL/g and/or a molecular weight in the range of 40-70 kDa, for example between 50-60 kDa. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the TCA/75:25 PLGA microparticle formulations, the range of TCA load percentage is between 22-28%. In one embodiment, the load percentage of TCA in the microparticles is 25%.

The microparticles in the TCA PLGA microparticle formulations can be formulated using PLGA polymers having a range of molecular weights from 40 to 70 kDa, most preferably from 50 to 60 kDa and range of inherent viscosities from 0.5 to 0.5 dL/g, most preferably from 0.38 to 0.42 dL/g.

For the TCA/75:25 PLGA microparticle formulations, the total dose of corticosteroid contained in the microparticles is in the range of 10-90 mg, where TCA is between 22-28% of the microparticle (i.e., when TCA is 25% of the microparticle, the microparticle is in the range of 40-360 mgs, when TCA is 22% of the microparticle, the microparticle is in the range of 45.5-409.1 mgs, when TCA is 28% of the microparticle, the microparticle is in the range of 35.7-321.4 mgs, and so on for all values between 22-28% load dose). In some embodiments, total dose of corticosteroid contained in the microparticles is in a range selected from 10-80 mg, 10-70 mg, 10-60 mg, 10-50 mg, 10-40 mg, 10-30 mg, 10-20 mg, 20-90 mg, 20-80 mg, 20-70 mg, 20-60 mg, 20-50 mg, 20-40 mg, 20-30 mg, 20-20 mg, 20-10 mg, 20-0 mg, 30-90 mg, 30-80 mg, 30-70 mg, 30-60 mg, 30-50 mg, 30-40 mg, 30-30 mg, 30-20 mg, 30-10 mg, 30-0 mg, 40-90 mg, 40-80 mg, 40-70 mg, 40-60 mg, 40-50 mg, 40-40 mg, 40-30 mg, 40-20 mg, 40-10 mg, 40-0 mg, 50-90 mg, 50-80 mg, 50-70 mg, 50-60 mg, 50-50 mg, 50-40 mg, 50-30 mg, 50-20 mg, 50-10 mg, 50-0 mg, 60-90 mg, 60-80 mg, 60-70 mg, 60-60 mg, 60-50 mg, 60-40 mg, 60-30 mg, 60-20 mg, 60-10 mg, 60-0 mg, 70-90 mg, 70-80 mg, 70-70 mg, 70-60 mg, 70-50 mg, 70-40 mg, 70-30 mg, 70-20 mg, 70-10 mg, 70-0 mg, 80-90 mg, 80-80 mg, 80-70 mg, 80-60 mg, 80-50 mg, 80-40 mg, 80-30 mg, 80-20 mg, 80-10 mg, 80-0 mg.

In some embodiments of the TCA/75:25 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes triamcinolone acetonide (TCA) and a microparticle made using 75:25 PLGA formulation and containing 10-20% triblock (PEG-PLGA-PEG) having an inherent viscosity in the range from 0.6 to 0.8 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The

diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes triamcinolone acetoneide (TCA) and a microparticle made using 75:25 PLGA formulation with two PLGA polymers, one of low molecular weight and one of high molecular weight in a two to one ratio, respectively. The low molecular weight PLGA has a molecular weight of range of 15-35 kDa and an inherent viscosity range from 0.2 to 0.35 dL/g and the high molecular weight PLGA has a range of 70-95 kDa and an inherent viscosity range of 0.5 to 0.70 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

These TCA microparticle formulations, preparations, and populations thereof, when administered to a patient, exhibit reduced undesirable side effects in patient, for example, undesirable effects on a patient's cartilage or other structural tissue, as compared to the administration, for example administration into the intra-articular space of a joint, of an equivalent amount of TCA absent any microparticle or other type of incorporation, admixture, or encapsulation.

In another embodiment, the corticosteroid microparticle formulation includes a Class A, C, or D corticosteroid and a microparticle made using 50:50 PLGA formulation. For example, in some embodiments, the Class A corticosteroid is prednisolone. In some embodiments, the Class C corticosteroid is betamethasone. In some embodiments, the Class D corticosteroid is fluticasone or fluticasone propionate. In these Class A, C, or D corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 μ m, or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the Class A and/or Class C PLGA microparticle formulations, the range of corticosteroid load percentage is between 10-40%, for example, between 15%-30%. For the Class D PLGA microparticle formulations, the range of corticosteroid load percentage is between 8-20%.

The microparticles in the Class A, C or D PLGA microparticle formulations can be formulated using PLGA polymers having a range of inherent viscosities from 0.35 to 0.5 dL/g and approximated molecular weights from 40 kDa to 70 kDa.

These Class A, C or D corticosteroid microparticle formulations, preparations, and populations thereof, when administered to a patient, exhibit reduced undesirable side effects in patient, for example, undesirable effects on a patient's cartilage or other structural tissue, as compared to the administration, for example administration into the intra-articular space of a joint, of an equivalent amount of the Class A, C or D corticosteroid absent any microparticle or other type of incorporation, admixture, or encapsulation.

The invention provides populations of microparticles including a Class A corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsu-

lated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid is between 15% to 30% of the microparticles.

The invention also provides controlled or sustained release preparations of a Class A corticosteroid including a lactic acid-glycolic acid copolymer microparticle containing the Class A corticosteroid, wherein the Class A corticosteroid is between 10% to 40%, for example between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention provides formulations that include (a) controlled- or sustained-release microparticles including a Class A corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid is between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.35 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 60:40 to 45:55; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped

In some embodiments, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid from the range of about 60:40 to 45:55. In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 50:50.

In some embodiments, the Class A corticosteroid is prednisolone or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, total dose of the Class A corticosteroid contained in the microparticles is in a range selected from 10-250 mg, where the Class A corticosteroid is between 10-40%, for example, between 15-30% of the microparticle (i.e., when the corticosteroid is 10% of the microparticle, the microparticle is in the range of 100-2500 mgs, when the corticosteroid is 15% of the microparticle, the microparticle is in the range of 66.7-1666.7 mgs, when the corticosteroid is 20% of the microparticle, the microparticle is in the range of 50-1250 mgs, when the corticosteroid is 25% of the microparticle, the microparticle is in the range of 40-1000 mgs, when the corticosteroid is 30% of the microparticle, the microparticle is in the range of 33.3-833.3 mgs, when the corticosteroid is 40% of the microparticle, the microparticle is in the range of 25-625 mgs and so on for all values between 10-40% load dose). For example, in some embodiments, the total dose of corticosteroid is in the range of 10-225 mg, 10-200 mg, 10-175 mg, 10-150 mg, 10-120 mg, 10-100 mg, 10-75 mg, 10-50 mg, 10-25 mg, 20-250 mg, 20-225 mg, 20-200 mg, 20-175 mg, 20-150 mg, 20-125 mg, 20-100 mg, 20-75 mg, 20-50 mg, 30-250 mg, 30-225 mg, 30-200 mg, 30-175 mg, 30-150 mg, 30-120 mg, 30-100 mg, 30-75 mg, 30-50 mg, 40-250 mg, 40-225 mg, 40-200 mg, 40-175 mg, 40-150 mg, 40-120 mg, 40-100 mg, 40-75 mg, 50-250 mg, 50-225 mg, 50-200 mg, 50-175 mg, 50-150 mg, 50-120 mg, 50-100 mg, 50-75 mg, 60-250 mg, 60-225 mg, 60-200 mg, 60-175 mg, 60-150 mg, 60-120 mg, 60-100 mg, 60-75 mg, 70-250 mg, 70-225 mg, 70-200 mg, 70-175 mg, 70-150 mg, 70-120 mg, 70-100 mg, 80-250 mg, 80-225 mg, 80-200 mg, 80-175 mg, 80-150 mg, 80-120 mg, 80-100 mg, 90-250 mg, 90-225 mg, 90-200 mg, 90-175 mg, 90-150 mg, or 90-120 mg. In some embodiments, the Class A corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μ m to 100 μ m, for example, the microparticles have a mean diameter in the range of 20-100

μM , 20-90 μM , 30-100 μM , 30-90 μM , or 10-90 μM . It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes prednisolone and a microparticle made using 50:50 PLGA formulation having a molecular weight in the range of 40 kDa to 70 kDa. In these prednisolone/50:50 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μM . In some embodiments, the microparticles have a mean diameter in the range of 20-100 μM , 20-90 μM , 30-100 μM , 30-90 μM , or 10-90 μM .

For the prednisolone/50:50 PLGA microparticle formulations, the range of prednisolone load percentage is between 10-40%, for example, between 15-30%.

In some embodiments of the prednisolone/50:50 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

The invention provides populations of microparticles including a Class C corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid is between 10% to 40% of the microparticles, for example between 15% to 30% of the microparticles.

The invention also provides controlled or sustained release preparations of a Class C corticosteroid including a lactic acid-glycolic acid copolymer microparticle containing the Class C corticosteroid, wherein the Class C corticosteroid is between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention provides formulations that include (a) controlled- or sustained-release microparticles having a Class C corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid is between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.35 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 60:40 to 45:55; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped.

In one embodiment of these populations, preparations and/or formulations, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid from the range of about

60:40 to 45:55. In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 50:50.

In some embodiments, the Class C corticosteroid is betamethasone or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, total dose of the Class C corticosteroid contained in the microparticles is in a range selected from 2-250 mg, where the Class C corticosteroid is between 10-40%, for example, between 15-30% of the microparticle (i.e., when the corticosteroid is 10% of the microparticle, the microparticle is in the range of 20-2500 mgs, when the corticosteroid is 15% of the microparticle, the microparticle is in the range of 13.3-1666.7 mgs, when the corticosteroid is 20% of the microparticle, the microparticle is in the range of 10-1250 mgs, when the corticosteroid is 25% of the microparticle, the microparticle is in the range of 8-1000 mgs, when the corticosteroid is 30% of the microparticle, the microparticle is in the range of 6.67-833.3 mgs, when the corticosteroid is 40% of the microparticle, the microparticle is in the range of 5-625 mgs and so on for all values between 10-40% load dose). For example, in some embodiments, the total dose of corticosteroid is in the range of 2-225 mg, 2-200 mg, 2-175 mg, 2-150 mg, 2-120 mg, 2-100 mg, 2-75 mg, 2-60 mg, 2-55 mg, 2-50 mg, 2-45 mg, 2-40 mg, 2-35 mg, 2-30 mg, 2-25 mg, 2-20 mg, 2-15 mg, 2-10 mg, 4-225 mg, 4-200 mg, 4-175 mg, 4-150 mg, 4-120 mg, 4-100 mg, 4-75 mg, 4-60 mg, 4-55 mg, 4-50 mg, 4-45 mg, 4-40 mg, 4-35 mg, 4-30 mg, 4-25 mg, 4-20 mg, 4-15 mg, 4-10 mg, 5-225 mg, 5-200 mg, 5-175 mg, 5-150 mg, 5-120 mg, 5-100 mg, 5-75 mg, 5-60 mg, 5-55 mg, 5-50 mg, 5-45 mg, 5-40 mg, 5-35 mg, 5-30 mg, 5-25 mg, 5-20 mg, 5-15 mg, 5-10 mg, 6-225 mg, 6-200 mg, 6-175 mg, 6-150 mg, 6-120 mg, 6-100 mg, 6-75 mg, 6-60 mg, 6-55 mg, 6-50 mg, 6-45 mg, 6-40 mg, 6-35 mg, 6-30 mg, 6-25 mg, 6-20 mg, 6-15 mg, 6-10 mg, 8-225 mg, 8-200 mg, 8-175 mg, 8-150 mg, 8-120 mg, 8-100 mg, 8-75 mg, 8-60 mg, 8-55 mg, 8-50 mg, 8-45 mg, 8-40 mg, 8-35 mg, 8-30 mg, 8-25 mg, 8-20 mg, 8-15 mg, 8-10 mg, 10-225 mg, 10-200 mg, 10-175 mg, 10-150 mg, 10-120 mg, 10-100 mg, 10-75 mg, 10-50 mg, 10-25 mg, 20-250 mg, 20-225 mg, 20-200 mg, 20-175 mg, 20-150 mg, 20-125 mg, 20-100 mg, 20-75 mg, 20-50 mg, 30-250 mg, 30-225 mg, 30-200 mg, 30-175 mg, 30-150 mg, 30-120 mg, 30-100 mg, 30-75 mg, 30-50 mg, 40-250 mg, 40-225 mg, 40-200 mg, 40-175 mg, 40-150 mg, 40-120 mg, 40-100 mg, 40-75 mg, 50-250 mg, 50-225 mg, 50-200 mg, 50-175 mg, 50-150 mg, 50-120 mg, 50-100 mg, 50-75 mg, 60-250 mg, 60-225 mg, 60-200 mg, 60-175 mg, 60-150 mg, 60-120 mg, 60-100 mg, 60-75 mg, 70-250 mg, 70-225 mg, 70-200 mg, 70-175 mg, 70-150 mg, 70-120 mg, 70-100 mg, 80-250 mg, 80-225 mg, 80-200 mg, 80-175 mg, 80-150 mg, 80-120 mg, 80-100 mg, 90-250 mg, 90-225 mg, 90-200 mg, 90-175 mg, 90-150 mg, or 90-120 mg. In some embodiments, the Class C corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μm to 100 μm , for example, the microparticles have a mean diameter in the range of 20-100 μM , 20-90 μM , 30-100 μM , 30-90 μM , or 10-90 μM . It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of

PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes betamethasone and a microparticle made using 50:50 PLGA formulation having a molecular weight in the range of 40 kDa to 70 kDa. In these betamethasone/50:50 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 μ m, or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the betamethasone/50:50 PLGA microparticle formulations, the range of prednisolone load percentage is between 10-40%, for example, between 15-30%.

In some embodiments of the betamethasone/50:50 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

The invention provides populations of microparticles including a Class D corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid is between 8% to 20% of the microparticles, for example, between 10% to 20% of the microparticles.

The invention also provides controlled or sustained release preparation of a Class D corticosteroid including a lactic acid-glycolic acid copolymer microparticle containing the Class D corticosteroid, wherein the Class D corticosteroid is between 8% to 20%, for example, between 10% to 20% of the microparticles of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention provides formulations including (a) controlled- or sustained-release microparticles having a Class D corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid is between 8% to 20% of the microparticles, for example, between 10% to 20% of the microparticles, and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.35 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 60:40 to 45:55; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped.

In one embodiment of these populations, preparations and/or formulations, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid from the range of about 60:40 to 45:55. In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 50:50.

In some embodiments, the Class D corticosteroid is fluticasone propionate, fluticasone, or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, total dose of the Class D

corticosteroid contained in the microparticles is in a range selected from 1-250 mg, where the Class D corticosteroid is between 8-20% of the microparticle (i.e., when the corticosteroid is 8% of the microparticle, the microparticle is in the range of 12.5-3125 mgs, when the corticosteroid is 10% of the microparticle, the microparticle is in the range of 10-2500 mgs, when the corticosteroid is 15% of the microparticle, the microparticle is in the range of 6.67-1666.7 mgs, when the corticosteroid is 20% of the microparticle, the microparticle is in the range of 5-1250 mgs, and so on for all values between 10-20% load dose). For example, in some embodiments, the total dose of corticosteroid is in the range of 1-225 mg, 1-200 mg, 1-175 mg, 1-150 mg, 1-120 mg, 1-100 mg, 1-75 mg, 1-60 mg, 1-55 mg, 1-50 mg, 1-45 mg, 1-40 mg, 1-35 mg, 1-30 mg, 1-25 mg, 1-20 mg, 1-15 mg, 1-10 mg, 2-225 mg, 2-200 mg, 2-175 mg, 2-150 mg, 2-120 mg, 2-100 mg, 2-75 mg, 2-60 mg, 2-55 mg, 2-50 mg, 2-45 mg, 2-40 mg, 2-35 mg, 2-30 mg, 2-25 mg, 2-20 mg, 2-15 mg, 2-10 mg, 3-225 mg, 3-200 mg, 3-175 mg, 3-150 mg, 3-120 mg, 3-100 mg, 3-75 mg, 3-60 mg, 3-55 mg, 3-50 mg, 3-45 mg, 3-40 mg, 3-35 mg, 3-30 mg, 3-25 mg, 3-20 mg, 3-15 mg, 3-10 mg, 4-225 mg, 4-200 mg, 4-175 mg, 4-150 mg, 4-120 mg, 4-100 mg, 4-75 mg, 4-60 mg, 4-55 mg, 4-50 mg, 4-45 mg, 4-40 mg, 4-35 mg, 4-30 mg, 4-25 mg, 4-20 mg, 4-15 mg, 4-10 mg, 5-225 mg, 5-200 mg, 5-175 mg, 5-150 mg, 5-120 mg, 5-100 mg, 5-75 mg, 5-60 mg, 5-55 mg, 5-50 mg, 5-45 mg, 5-40 mg, 5-35 mg, 5-30 mg, 5-25 mg, 5-20 mg, 5-15 mg, 5-10 mg, 6-225 mg, 6-200 mg, 6-175 mg, 6-150 mg, 6-120 mg, 6-100 mg, 6-75 mg, 6-60 mg, 6-55 mg, 6-50 mg, 6-45 mg, 6-40 mg, 6-35 mg, 6-30 mg, 6-25 mg, 6-20 mg, 6-15 mg, 6-10 mg, 8-225 mg, 8-200 mg, 8-175 mg, 8-150 mg, 8-120 mg, 8-100 mg, 8-75 mg, 8-60 mg, 8-55 mg, 8-50 mg, 8-45 mg, 8-40 mg, 8-35 mg, 8-30 mg, 8-25 mg, 8-20 mg, 8-15 mg, 8-10 mg, 10-225 mg, 10-200 mg, 10-175 mg, 10-150 mg, 10-120 mg, 10-100 mg, 10-75 mg, 10-50 mg, 10-25 mg, 20-250 mg, 20-225 mg, 20-200 mg, 20-175 mg, 20-150 mg, 20-125 mg, 20-100 mg, 20-75 mg, 20-50 mg, 30-250 mg, 30-225 mg, 30-200 mg, 30-175 mg, 30-150 mg, 30-120 mg, 30-100 mg, 30-75 mg, 30-50 mg, 40-250 mg, 40-225 mg, 40-200 mg, 40-175 mg, 40-150 mg, 40-120 mg, 40-100 mg, 40-75 mg, 50-250 mg, 50-225 mg, 50-200 mg, 50-175 mg, 50-150 mg, 50-120 mg, 50-100 mg, 50-75 mg, 60-250 mg, 60-225 mg, 60-200 mg, 60-175 mg, 60-150 mg, 60-120 mg, 60-100 mg, 60-75 mg, 70-250 mg, 70-225 mg, 70-200 mg, 70-175 mg, 70-150 mg, 70-120 mg, 70-100 mg, 80-250 mg, 80-225 mg, 80-200 mg, 80-175 mg, 80-150 mg, 80-120 mg, 80-100 mg, 90-250 mg, 90-225 mg, 90-200 mg, 90-175 mg, 90-150 mg, or 90-120 mg. In some embodiments, the Class D corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μ m to 100 μ m, for example, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 μ m, or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes fluticasone propionate or fluticasone, and a micro-

particle made using 50:50 PLGA formulation having a molecular weight in the range of 40 kDa to 70 kDa. In these fluticasone or fluticasone propionate/50:50 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the fluticasone or fluticasone propionate/50:50 PLGA microparticle formulations, the range of prednisolone load percentage is between 10-20%.

In some embodiments of the fluticasone or fluticasone propionate/50:50 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

These embodiments of corticosteroid microparticle formulations have been selected because the combination of class of corticosteroid, type of microparticle, molecular weight of polymers used to create the microparticles lactide:glycolide molar ratio, and/or load percentage of the corticosteroid exhibit the desired release kinetics. These embodiments also exhibit the desired release kinetics with minimal prolonged HPA axis suppression.

The invention provides methods of treating pain or inflammation in a patient comprising administering to said patient a therapeutically effective amount of a population of microparticles selected from the following populations: (i) a population of microparticles comprising a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles; (ii) a population of microparticles comprising a Class A corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles; (iii) a population of microparticles comprising a Class C corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid comprises between 15% to 30% of the microparticles; and (iv) a population of microparticles comprising a Class D corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles. In some embodiments, the population of microparticles releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). In some embodiments, the population of microparticles releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-administration. In some embodiments, the population of microparticles releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration. In some embodiments, the population of microparticles releases the corticosteroid in a controlled or

sustained release manner such that the levels of cortisol suppression are negligible at any time post-administration.

The invention provides methods of treating pain or inflammation in a patient comprising administering to said patient a therapeutically effective amount of a controlled or sustained release preparation selected from the following preparations: (i) a controlled or sustained release preparation of a Class B corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class B corticosteroid, wherein the Class B corticosteroid comprises between 22% to 28% of the lactic acid-glycolic acid copolymer microparticle matrix; (ii) a controlled or sustained release preparation of a Class A corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class A corticosteroid, wherein the Class A corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; (iii) a controlled or sustained release preparation of a Class C corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class C corticosteroid, wherein the Class C corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; and (iv) a controlled or sustained release preparation of a Class D corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class D corticosteroid, wherein the Class D corticosteroid comprises between 8% to 20% of the lactic acid-glycolic acid copolymer microparticle matrix. In some embodiments, the controlled or sustained release preparation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). In some embodiments, the controlled or sustained release preparation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-administration. In some embodiments, the controlled or sustained release preparation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration. In some embodiments, the controlled or sustained release preparation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible at any time post-administration.

The invention provides methods of treating pain or inflammation in a patient comprising administering to said patient a therapeutically effective amount of a formulation selected from the following preparations: (i) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class B corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.5 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 80:20 to 60:40; (ii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class A corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 45:55; (iii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class C corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the

Class C corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 45:55; and (iv) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class D corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 45:55. In some embodiments, the formulation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). In some embodiments, the formulation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-administration. In some embodiments, the formulation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration. In some embodiments, the formulation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible at any time post-administration.

In some embodiments, the population of microparticles, the controlled or sustained release preparation or formulation is administered as one or more intra-articular injections. In some embodiments, the patient has osteoarthritis, rheumatoid arthritis, acute gouty arthritis, and synovitis. In some embodiments, the patient has acute bursitis, sub-acute bursitis, acute nonspecific tenosynovitis, or epicondylitis.

In one aspect, a method of treating pain and/or inflammation in a joint of a patient is provided that includes administering intra-articularly (e.g., by one or more injections) to a patient with joint disease (e.g., osteoarthritis or rheumatoid arthritis) a formulation that contains one or more corticosteroids, such as those formulations described herein. Therapeutically effective amounts of the one or more corticosteroids are released for a period of time at a rate that does not suppress (e.g., adversely and/or measurably) the HPA axis.

In another aspect, a method of treating pain and/or inflammation in a joint of a patient is provided that includes administering intra-articularly (e.g., by one or more injections) a therapeutically effective amount of one or more corticosteroids in a formulation to a patient with joint disease (e.g., osteoarthritis or rheumatoid arthritis). The formulation has a sustained release microparticle formulation that may or may not release detectable levels of corticosteroid for a length of time following administration and that releases a detectable amount of corticosteroid(s) following administration, where the rate of corticosteroid release from the sustained release microparticle formulation does not adversely suppress the HPA axis. In some embodiments, corticosteroid released from the sustained release microparticle formulation will not measurably suppress the HPA axis.

According to certain embodiments of the foregoing methods, the formulation comprises a population of biodegradable polymer microparticles that contain the corticosteroids. In some embodiments, the corticosteroids are 2% to 75% (w/w) of the microparticles, preferably about 5% to 50% (w/w) of the microparticles, and more preferably 5% to 40% or 10% to 30% (w/w) of the microparticles. In some embodiments, the

microparticles have a mass mean diameter of between 10 μ m to 100 μ m. In some embodiments, the microparticles are formed from a hydrogel, hyaluronic acid, PLA or PLGA. For example, the microparticles are formed from PLGA with a lactide to glycolide co-polymer ratio of about 45:55 to about 80:20. In some embodiments, the corticosteroid is betamethasone, dexamethasone, triamcinolone acetonide, triamcinolone hexacetonide, prednisolone, methylprednisolone, budesonide, mometasone, ciclesonide, fluticasone, salts thereof, esters thereof or combinations thereof.

In yet another aspect, a composition is provided that includes a population of biodegradable polymer microparticles that contain corticosteroid(s). For example, the corticosteroid is betamethasone, dexamethasone, triamcinolone acetonide, triamcinolone hexacetonide, prednisolone, methylprednisolone, budesonide, mometasone, ciclesonide, fluticasone, salts thereof, esters thereof or combinations thereof. When the composition is administered intra-articularly (e.g., by one or more injections), a therapeutically effective amount of corticosteroid(s) is released for a period of time at a rate that does not suppress the HPA axis. In some embodiments, the corticosteroid(s) released will not adversely suppress the HPA axis. In some embodiments, the corticosteroid(s) released will not measurably suppress the HPA axis.

In yet a further aspect, a composition is provided that includes a population of biodegradable polymer microparticles that contain corticosteroid(s). For example, the corticosteroid is betamethasone, dexamethasone, triamcinolone acetonide, triamcinolone hexacetonide, prednisolone, methylprednisolone, budesonide, mometasone, ciclesonide, fluticasone, salts thereof, esters thereof or combinations thereof. When the composition is administered intra-articularly (e.g., by one or more injections), therapeutically effective amounts of corticosteroid(s) are released following administration from a first component for a first length of time and from a sustained release component for a second length of time. Furthermore, the rate of corticosteroid(s) released from the sustained release component does not suppress the HPA axis. In some embodiments, the corticosteroid(s) released from the sustained release component during the second length of time will not adversely suppress the HPA axis. In some embodiments, the corticosteroid(s) released from the sustained release component during the second length of time will not measurably suppress the HPA axis. In some embodiments, the first component comprises a corticosteroid containing solution or suspension. In some embodiments, the first component contains a corticosteroid that is different from that of the sustained release component. In other embodiments, the same corticosteroid is used in both the first and sustained release components.

According to certain embodiments of the foregoing compositions, the corticosteroids are 2% to 75% (w/w) of the microparticles, preferably about 5% to 50% (w/w) of the microparticles, and more preferably 5% to 40% (w/w) of the microparticles. In some embodiments, the microparticles have a mass mean diameter of between 10 μ m to 100 μ m. In some embodiments, the microparticles are formed from a hydrogel, hyaluronic acid, PLA or PLGA. For example, the microparticles are formed from PLGA with a lactide to glycolide co-polymer ratio of about 45:55 to about 80:20. In some embodiments, the compositions further comprise a corticosteroid containing solution or suspension. In some embodiments, the corticosteroid containing solution or suspension contains a corticosteroid that is different from that found in the microparticles.

The invention also provides methods of slowing, arresting or reversing progressive structural tissue damage associated

with chronic inflammatory disease in a patient comprising administering to said patient a therapeutically effective amount of a population of microparticles selected from the following populations: (i) a population of microparticles comprising a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles; (ii) a population of microparticles comprising a Class A corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles; (iii) a population of microparticles comprising a Class C corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid comprises between 15% to 30% of the microparticles; and (iv) a population of microparticles comprising a Class D corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles. In some embodiments, the population of microparticles releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

The invention also provides methods of slowing, arresting or reversing progressive structural tissue damage associated with chronic inflammatory disease in a patient comprising administering to said patient a therapeutically effective amount of a controlled or sustained release preparation selected from the following preparations: (i) a controlled or sustained release preparation of a Class B corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class B corticosteroid, wherein the Class B corticosteroid comprises between 22% to 28% of the lactic acid-glycolic acid copolymer microparticle matrix; (ii) a controlled or sustained release preparation of a Class A corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class A corticosteroid, wherein the Class A corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; (iii) a controlled or sustained release preparation of a Class C corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class C corticosteroid, wherein the Class C corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; and (iv) a controlled or sustained release preparation of a Class D corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class D corticosteroid, wherein the Class D corticosteroid comprises between 8% to 20% of the lactic acid-glycolic acid copolymer microparticle matrix. In some embodiments, the controlled or sustained release preparation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

The invention also provides methods of slowing, arresting or reversing progressive structural tissue damage associated with chronic inflammatory disease in a patient comprising administering to said patient a therapeutically effective amount of a formulation selected from the following preparations: (i) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class B corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to

70 kDa; (2) an inherent viscosity in the range of 0.3 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 80:20 to 60:40; (ii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class A corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 50:50; (iii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class C corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 50:50; and (iv) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class D corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 50:50. In some embodiments, the formulation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

In some embodiments, the population of microparticles, the controlled or sustained release preparation or formulation is administered as one or more intra-articular injections. In some embodiments, the patient has osteoarthritis, rheumatoid arthritis, acute gouty arthritis, and synovitis. In some embodiments, the patient has acute bursitis, sub-acute bursitis, acute nonspecific tenosynovitis, or epicondylitis.

The invention also provides methods to slow, arrest, reverse or otherwise inhibit progressive structural tissue damage associated with chronic inflammatory disease, for example, damage to cartilage associated with osteoarthritis. In one embodiment, the method includes the administration to a patient, for example local administration, of a therapeutically effective amount of one or more corticosteroids in a formulation, wherein the formulation releases the corticosteroid(s) for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). The methods to assess the effect of corticosteroid formulations on disease progression include controlled clinical studies that assess clinical end points and for employ imaging technologies such as, for example Magnetic Resonance Imaging (MRI), to determine effects on the structure in chronically inflamed tissues, for example the effects on cartilage volume and other articular and peri-articular structures in osteoarthritis and rheumatoid arthritis. (See e.g., Eckstein F, et al. "Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment." *Osteoarthritis Cartilage* 14 Suppl A (2006): A46-75; Lo G H, et al. "Bone marrow lesions in the knee are associated with increased local bone density." *Arthritis Rheum* 52 (2005): 2814-21; and Lo G H, et al. "The ratio of medial to lateral tibial plateau bone mineral density and compartment-specific tibiofemoral osteoarthritis." *Osteoarthritis Cartilage* 14 (2006): 984-90 the contents of each of which are hereby incorporated by reference in their entirety.) The corticoster-

oid microparticle formulations provided herein appear to exhibit little to no negative effects, e.g., structural tissue damage, and from preliminary data and studies described in the Examples below, these corticosteroid microparticle formulations appear to have a positive effect, e.g., slowing, arresting or reversing structural tissue damage.

The invention also provides methods of treating pain and/or inflammation of a patient by administering to the patient a therapeutically effective amount of one or more corticosteroids in a formulation, wherein the formulation releases the corticosteroid(s) for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

The invention also provides methods of manufacturing the corticosteroid microparticle formulations. The microparticle formulations provided herein can be manufactured using any of a variety of suitable methods.

For the Class B corticosteroid microparticle formulations, in some embodiments, the microparticles are manufactured as described in the Examples provided below. For the Class B corticosteroid microparticle formulations, in some embodiments, the microparticles are manufactured as described in U.S. Pat. No. 7,261,529 and U.S. Pat. No. 7,758,778, the contents of each of which are hereby incorporated by reference in their entirety. For example, the microparticles are manufactured using a solvent evaporation process wherein the Class B corticosteroid is dispersed in a lactic acid-glycolic acid copolymer organic solution and the mixture is treated to remove the solvent from the mixture, thereby producing microparticles.

In some embodiments, the solvent evaporation process utilizes a spray drying or fluid bed apparatus to remove the solvent and produce microparticles. In some embodiments, the solvent evaporation process utilizes a spinning disk. For example, the spinning disk is the spinning disk as described in U.S. Pat. No. 7,261,529 and U.S. Pat. No. 7,758,778.

For the Class B corticosteroid microparticle formulations, in some embodiments where the Class B corticosteroid is TCA, the microparticles are manufactured using a solid in oil in water emulsion process wherein TCA is dispersed in a lactic acid-glycolic acid copolymer organic solution and added to an aqueous solvent to produce microparticles.

For the Class A, C and/or D corticosteroid microparticle formulations, in some embodiments, the microparticles are manufactured as described in the Examples provided below. For Class A, C and/or D corticosteroid formulations, in some embodiments, the microparticles are manufactured as described in PCT Publication No. WO 95/13799, the contents of which are hereby incorporated by reference in their entirety. For example, the microparticles are manufactured using a solid in oil in water emulsion process wherein the Class A corticosteroid, Class C corticosteroid and/or Class D corticosteroid is dispersed in a lactic acid-glycolic acid copolymer organic solution and added to an aqueous solvent to produce microparticles.

It is contemplated that whenever appropriate, any embodiment of the present invention can be combined with one or more other embodiments of the present invention, even though the embodiments are described under different aspects of the present invention.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph depicting the intra-articular concentrations (top solid line) and the systemic concentrations (bottom solid line) of the glucocorticoid administered according to certain embodiments of the present invention following intra-

articular injection. The systemic glucocorticoid concentration associated with clinically significant suppression of the HPA axis is shown as the bottom dotted line. The top dotted line represents the minimal intra-articular concentration required to maintain efficacy (defined as relief of pain and inflammation, or slowing, arrest, or reversal of structural damage to tissues caused by inflammatory diseases. Sustained release of the corticosteroid provides sufficient intra-articular concentrations to maintain efficacy in the longer term, and has transient, clinically insignificant effect on the HPA axis.

FIG. 2 is a graph depicting the change in sensitivity over time to suppression of endogenous cortisol production (EC_{50} (ng/mL) vs. time) for triamcinolone acetate 40 mg given by intra-articular administration.

FIG. 3 is a graph depicting the change in sensitivity over time to suppression of endogenous cortisol production (EC_{50} (ng/mL) vs. time) for various corticosteroids administered as a single, intra-articular injection in the listed dose.

FIG. 4 is a graph depicting plasma levels of endogenous cortisol over time, without (Column 1) adjustment for a change in the sensitivity of the HPA axis after intra-articular corticosteroids and with (Column 2) adjustment for a change in the sensitivity of the HPA axis after intra-articular corticosteroids. These data demonstrate that the sensitivity of the HPA axis varies with corticosteroid, dose, and time with clinically important implications for the selection of doses for sustained delivery into an intra-articular space.

FIG. 5 is a graph depicting the cumulative percent release of a nominal 25% (w/w) triamcinolone acetate in PLGA 75:25 microparticles.

FIG. 6 is a graph depicting the calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 25% TCA PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 7 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 25% TCA PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 8 is a graph depicting cumulative percent release of a second preparation of nominal 25% triamcinolone acetate in PLGA 75:25 microparticles using an alternate preparation.

FIG. 9 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using a second preparation of nominal 25% TCA PLGA 75:25 microparticles made by an alternate preparation. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 10 is a graph depicting: calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using a second preparation of nominal 25% TCA PLGA 75:25 microparticles made by an alternate preparation. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 11 is a graph depicting cumulative percent release of nominal 25% triamcinolone acetate in 5% PEG 1450/PLGA 75:25 microparticles.

FIG. 12 is a graph depicting cumulative percent release of nominal 25% triamcinolone acetonide in 10% PEG 3350/PLGA 75:25 microparticles.

FIG. 13 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 25% TCA 5% PEG 1450/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 14 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 25% TCA 10% PEG 3350/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 15 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 25% TCA 5% PEG 1450/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 16 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 25% TCA 10% PEG 3350/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 17 is a graph depicting cumulative percent triamcinolone acetonide release of nominal 40%, 25% 20%, 15% and 10% TCA containing PLGA 75:25 microparticles.

FIG. 18 is a graph depicting cumulative percent release of nominal 25% TCA PLGA 75:25 (29 kDa) and PLGA 75:25 (54 kDa) containing microparticles.

FIG. 19 is a graph depicting cumulative percent release of triamcinolone acetonide in PLGA 50:50 microparticle formulations.

FIG. 20 is a graph depicting cumulative percent release of nominal 28.6% triamcinolone acetonide in PLGA 75:25 plus Triblock microparticle formulations.

FIG. 21 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% TCA 10% Triblock/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 22 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% TCA 20% Triblock/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 23 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% TCA 10% Triblock/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 24 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% TCA 20% Triblock/PLGA 75:25

microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 25 is a graph depicting cumulative percent release of nominal 16.7% triamcinolone acetonide in mixed molecular weight PLGA 75:25 microparticle formulations.

FIG. 26 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 16.7% TCA mixed molecular weight PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 27 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 16.7% TCA mixed molecular weight PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 28 is a graph depicting cumulative percent release of nominal 28.6% triamcinolone acetonide in various polymer microparticle formulations.

FIG. 29 is a graph depicting cumulative percent release of nominal 28.6% Prednisolone in PLGA 50:50 microparticle formulation.

FIG. 30 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% PRED PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 31 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% PRED PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 32 is a graph depicting cumulative percent release of nominal 28.6% Betamethasone PLGA 50:50 microparticle formulation.

FIG. 33 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% BETA PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 34 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% BETA PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 35 is a graph depicting cumulative percent release of nominal 16.7% Fluticasone Propionate PLGA 50:50 microparticle formulation.

FIG. 36 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 16.7% FLUT PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol

inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 37 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 16.7% FLUT PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 38 is a graph depicting cumulative percent release of various Fluticasone Propionate PLGA microparticle formulations.

FIG. 39 is a graph depicting cumulative percent release of nominal 28.6% DEX PLGA 50:50 microparticle formulation.

FIG. 40 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression and does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% DEX PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIGS. 41A-41D are a series of graphs depicting the mean concentration-time profiles of various doses of TCA IR and FX006 in rat plasma following single intra-articular doses. A microparticle formulation of TCA in 75:25 PLGA formulation microparticles, referred to as FX006, dosed at 1.125 mg resulted in a very slow absorption of TCA in the systemic circulation and a markedly lower C_{max} as compared to TCA IR. Concentrations for the first 72 hr are presented in FIGS. 41C and 41D on a larger time scale.

FIG. 42 is a graph depicting corticosteroid inhibition and recovery with TCA IR (immediate release) and FX006 (microparticle formulation) in rats.

FIG. 43 is a graph depicting the pharmacokinetic/pharmacodynamic (PK/PD) relationship of systemic TCA levels and corticosterone inhibition.

FIGS. 44A-44C are a series of graphs depicting the gait analysis scores, an indicator of pain, in rats injected with doses of either immediate release triamcinolone acetate (TCA IR) or TCA microparticles (FX006) in a model of osteoarthritis. In FIG. 44A, FX006 at 0.28, 0.12 and 0.03 mg (TCA doses) is expressed as TCA concentrations of the dosing formulation (4.67, 2 and 0.5 mg/ml). In FIG. 44B, FX006 at 0.28 mg (TCA dose) is expressed as TCA concentrations of the dosing formulation (4.67 mg/ml). Similarly, TCA IR at 0.03 mg is expressed as triamcinolone at 0.5 mg/ml. In FIG. 44C, FX006 at 0.28, 0.12 and 0.03 mg (TCA doses) is expressed as TCA concentrations of the dosing formulation (4.67, 2 and 0.5 mg/ml). Similarly, TCA IR at 0.06 and 0.03 mg is expressed as triamcinolone at 1 and 0.5 mg/ml.

FIG. 45 is a graph depicting peak pain response following repeated reactivations of arthritis in the right knee. All treatments were administered as a single IA dose in the right knee on Day 0.

FIG. 46 is a graph depicting the time course of corticosterone recovery for various groups in the rat study in a model of osteoarthritis.

FIGS. 47A-47B are a series of graphs depicting the plasma TCA concentration-time data for various groups in the rat study in a model of osteoarthritis. Only the groups that received injections of TCA microparticles (FX006 groups) are shown in FIG. 47B on an expanded scale.

FIG. 48 is a graph depicting the end-of-study histopathology scores for various treatment groups in the rat study in a model of osteoarthritis.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides compositions and methods for the treatment of pain and inflammation using corticosteroids. The compositions and methods provided herein use one or more corticosteroids in a microparticle formulation. The corticosteroid microparticle formulations provided herein are effective at treating pain and/or inflammation with minimal prolonged suppression of the HPA axis and/or other long term side effects of corticosteroid administration. The corticosteroid microparticle formulations provided herein are effective in slowing, arresting, reversing or otherwise inhibiting structural damage to tissues associated with progressive disease with minimal prolonged suppression of the HPA axis and/or other long term side effects of corticosteroid administration. The corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-injection. In some embodiments, the corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-injection. Thus, the corticosteroid microparticle formulations in these embodiments are effective in the absence of any significant HPA axis suppression. Administration of the corticosteroid microparticle formulations provided herein can result in an initial "burst" of HPA axis suppression, for example, within the first few days, within the first two days and/or within the first 24 hours post-injection, but by day 14 post-injection, suppression of the HPA axis is less than 35%.

The use of microparticles to administer corticosteroids is known (See, e.g., U.S. Patent Application Publication. No. 20080317805). In addition, corticosteroids are known to be useful for the symptomatic treatment of inflammation and pain. New data also suggest that synovitis may be associated with the structural damage, for example, the deterioration of cartilage and other peri-articular associated with the progression of osteoarthritis and rheumatoid arthritis. (See e.g., Hill C L, et al. "Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis." *Ann Rheum Dis* 66 (2007):1599-603; van den Berg W B, et al. "Synovial mediators of cartilage damage and repair in osteoarthritis." In: Brandt K D, Doherty M, Lohmander L S, eds. *Osteoarthritis*. Second ed. Oxford: Oxford University Press (2003):147-55; Ayral X, et al. "Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis—results of a 1 year longitudinal arthroscopic study in 422 patients." *Osteoarthritis Cartilage* 13 (2005):361-7; and Kirwan J R, et al. "Effects of glucocorticoids on radiological progression in rheumatoid arthritis." *Cochrane Database Syst Rev* 2007:CD006356).

The administration of corticosteroids, particularly for extended periods of time, can have a number of unwanted side effects. The HPA axis, the interdependent feedback mechanism between the hypothalamus, the pituitary gland and the adrenal cortex, may be suppressed by the administration of corticosteroids, leading to a variety of unwanted side effects. The extent of HPA axis suppression, and related inhibition of endogenous cortisol production, has been attributed to the potency of the corticosteroid, the dose, systemic concentration, protein binding, rate of elimination (Meibohm et al. "Mechanism-based PK/PD model for the lymphocytopenia induced by endogenous and exogenous corticosteroids." *Int J Clin Pharmacol Ther* 37(8) (1999):367-76) and, for one corticosteroid, a change in sensitivity of the HPA axis (Derendorf et al. "Clinical PK/PD modelling as a tool in drug develop-

ment of corticosteroids." *Int J Clin Pharmacol Ther.* 35(10) 1997: 481-8). Furthermore, intra-articular doses of corticosteroids associated with only limited anti-inflammatory and short-term analgesic benefit (Hepper et al. "The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies." *J Am Acad Orthop Surg.* 17(10) 2009: 638-46) have been associated with HPA axis suppression (Habib, "Systemic effects of intra-articular corticosteroids." *Clin Rheumatol.* 28(7) (2009): 749-56).

The changes in sensitivity to corticosteroid effects over time should alter clinical steroid dosing, but prior to the instant invention, this has not been understood.

The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present Specification will control.

DEFINITIONS

The terms below have the following meanings unless indicated otherwise.

An amount of a corticosteroid that does not "suppress the hypothalamic-pituitary-adrenal axis (HPA axis)" refers to the amount of the sustained release corticosteroid delivered locally to relieve pain due to inflammation, which provides a systemic concentration that will not have a clinically significant effect or "adverse effect" on the HPA axis. Suppression of the HPA axis is generally manifested by a reduction in endogenous glucocorticoid production. It is useful to consider both basal and augmented production of endogenous glucocorticoids. Under ordinary, "unstressed" conditions, glucocorticoid production occurs at a normal, basal level. There is some natural variation of production during the course of the 24-hour day. Under extraordinary, "stressed" conditions associated with, e.g., infection or trauma and the like, augmented endogenous production of glucocorticoids occurs. Endogenous cortisol production may be determined by measuring glucocorticoid concentrations in plasma, saliva, urine or by any other means known in the art. It is known that systemic concentrations of corticosteroids can suppress the HPA axis. For example, on day 3 after an intra-articular injection of 20 mg triamcinolone hexacetonide plasma levels, of approximately 3-4 ng/mL have been observed. These resulted in a transient but highly statistically significant 75% HPA-axis suppression (Derendorf et al., "Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration." *Clin Pharmacol Ther.* 39(3) (1986):313-7) which, however, does not necessarily portend complete HPA failure (Habib, "Systemic effects of intra-articular corticosteroids." *Clin Rheumatol* 28 (2009): 749-756, see p752 col. 1, para 2, final sentence). While such transient suppression is generally considered to be acceptable without clinically significant effect, more persistent suppression, i.e., weeks, would be deemed clinically detrimental. In embodiments of the present invention, administration of the formulation may result in a clinically acceptable HPA suppression, particularly during the initial release

period of the therapy. In some embodiments of the present invention, administration of the formulation will not result in any significant level of HPA suppression, including no detectable HPA suppression, particularly during the initial release period of the therapy. During the subsequent or sustained release period of the therapy, additional corticosteroid may be released into the plasma. However, the plasma levels during this period will generally be less than those during the initial release period, if any corticosteroid release occurs, and will not be associated with HPA axis suppression. Further, the adverse events associated with exogenous corticosteroid administration, e.g., hyperglycemia, hypertension, altered mood, etc. will generally not be observed. Preferably, the number of clinical adverse events during this period will not substantially exceed the number achieved by an immediate release formulation alone or by KENALOG™ or its bioequivalent and will, preferably, be fewer than during the prior, initial release period of the therapy, if any corticosteroid release occurs. Alternatively, one can determine the suppression of the formulation on HPA by measuring endogenous cortisol production. Thus, the formulation can be considered as avoiding clinically significant (or adverse) suppression of the HPA axis where the endogenous cortisol level is substantially the same in the steady state between a patient population receiving a therapeutically beneficial amount of an immediate release formulation and those receiving a therapeutically beneficial amount of a sustained release formulation. Such a formulation would be deemed to have no clinically significant effect on the HPA axis. Alternatively or additionally, a small but measurable reduction in steady-state glucocorticoid production can result from the formulation during the sustained release period of the therapy with adequate preservation of the augmented, stress response needed during infection or trauma can be deemed a clinically insignificant suppression of the HPA axis. Endogenous glucocorticoid production may be assessed by administering various doses of adrenocorticotropin hormone or by other tests known to those skilled in the art. Embodiments of the current invention provide for controlling the release of corticosteroid, as may be desired, to achieve either no measurable effect on endogenous glucocorticoid production or a target, or a measurable effect that is, however, without adverse clinical consequence. In this regard, it has been found that intra-articular doses of corticosteroids that suppress cortisol production by 20-35%, and sometimes more, provide very useful sustained anti-inflammatory and analgesic activity. These benefits are achieved without acute risks of hypoadrenalism and without excessive risks, after sustained intra-articular dosing, of developing an adrenal unresponsiveness in times of stress or of developing frank adrenal failure.

As shown further below, the studies presented herein have demonstrated that the HPA axis sensitivity appears to diminish with time, steroid, and dose. In this regard, it has been determined that standard doses of familiar corticosteroids, when examined from the viewpoint of steady-state HPA axis suppression (i.e., after desensitization has occurred), provide clinically useful benchmarks. For example, while oral prednisolone given at 20 mg QD produces a 73% cortisol suppression, even 5 mg QD (considered a "low dose") is associated with a 40% suppression of endogenous cortisol production. Doses at or below 5 mg of prednisolone per day are generally considered to be well tolerated and are not associated with clinically meaningful HPA axis suppression (La Rochelle et al., "Recovery of the hypothalamic-pituitary-adrenal (HPA) axis in patients with rheumatic diseases receiving low-dose prednisolone." *Am. J. Med.* 95 (1993): 258-264). Therefore, up to approximately 40% suppression will be clinically well

tolerated and very unlikely to be associated with importantly adverse clinical events such as hypoadrenalism or soft-tissue or bony or metabolic changes indicative of long-term glucocorticoid excess.

"Patient" refers to a human diagnosed with a disease or condition that can be treated in accordance to the inventions described herein. In some embodiments it is contemplated that the formulations described herein may also be used in horses.

"Delivery" refers to any means used to place the drug into a patient. Such means may include without limitation, placing matrices into a patient that release the drug into a target area. One of ordinary skill in the art recognizes that the matrices may be delivered by a wide variety of methods, e.g., injection by a syringe, placement into a drill site, catheter or canula assembly, or forceful injection by a gun type apparatus or by placement into a surgical site in a patient during surgery.

The terms "treatment" and "treating" a patient refer to reducing, alleviating, stopping, blocking, or preventing the symptoms of pain and/or inflammation in a patient. As used herein, "treatment" and "treating" includes partial alleviation of symptoms as well as complete alleviation of the symptoms for a time period. The time period can be hours, days, months, or even years.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, e.g., analgesia. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

"Site of a patient's pain" refers to any area within a body causing pain, e.g., a knee joint with osteoarthritis, nerve root causing sciatic pain, nerve fibers growing into annular tears in discs causing back pain, temporomandibular joint (TMJ) pain, for example TMJ pain associated with temporomandibular joint disorder (TMD) or pain radiating from epidural or perineural spaces. The pain perceived by the patient may result from inflammatory responses, mechanical stimuli, chemical stimuli, thermal stimuli, as well as allodynia.

Additionally, the site of a patient's pain can comprise one or multiple sites in the spine, such as between the cervical, thoracic, or lumbar vertebrae, or can comprise one or multiple sites located within the immediate area of inflamed or injured joints such as the shoulder, hip, or other joints.

A "biocompatible" material refers to a material that is not toxic to the human body, it is not carcinogenic and it should induce limited or no inflammation in body tissues. A "biodegradable" material refers to a material that is degraded by bodily processes (e.g., enzymatic) to products readily disposable by the body or absorbed into body tissue. The biodegraded products should also be biocompatible with the body. In the context of intra-articular drug delivery systems for corticosteroids, such polymers may be used to fabricate, without limitation: microparticles, micro-spheres, matrices, microparticle matrices, micro-sphere matrices, capsules, hydrogels, rods, wafers, pills, liposomes, fibers, pellets, or other appropriate pharmaceutical delivery compositions that a physician can administer into the joint. The biodegradable polymers degrade into non-toxic residues that the body easily removes or break down or dissolve slowly and are cleared from the body intact. The polymers may be cured ex-vivo forming a solid matrix that incorporates the drug for controlled release to an inflammatory region. Suitable biodegradable polymers may include, without limitation natural or synthetic biocompatible biodegradable material. Natural polymers include, but are not limited to, proteins such as

albumin, collagen, gelatin synthetic poly(aminoacids), and prolamines; glycosaminoglycans, such as hyaluronic acid and heparin; polysaccharides, such as alginates, chitosan, starch, and dextrans; and other naturally occurring or chemically modified biodegradable polymers. Synthetic biocompatible biodegradable materials include, but are not limited to, poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PG), polyhydroxybutyric acid, poly(trimethylene carbonate), polycaprolactone (PCL), polyvalerolactone, poly(alpha-hydroxy acids), poly(lactones), poly(amino-acids), poly(anhydrides), polyketals poly(arylates), poly(orthoesters), polyurethanes, polythioesters, poly(orthocarbonates), poly(phosphoesters), poly(ester-co-amide), poly(lactide-co-urethane, polyethylene glycol (PEG), polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer (polyactive), methacrylates, poly(N-isopropylacrylamide), PEO-PPO-PEO (plurionics), PEO-PPO-PAA copolymers, and PLGA-PEO-PLGA blends and copolymers thereof and any combinations thereof. The biocompatible biodegradable material can include a combination of biocompatible biodegradable materials. For example, the biocompatible biodegradable material can be a triblock, or other multi-block, formation where a combination of biocompatible biodegradable polymers are joined together. For example, the triblock can be PLGA-PEG-PLGA.

Diseases that May be Treated Using the Formulations of this Invention

Descriptions of various embodiments of the invention are given below. Although these embodiments are exemplified with reference to treat joint pain associated with osteoarthritis, rheumatoid arthritis and other joint disorders, it should not be inferred that the invention is only for these uses. Rather, it is contemplated that embodiments of the present invention will be useful for treating other forms of joint pain by administration into articular and periarticular spaces. In addition, it will be understood that for some embodiments injection near a joint may be equivalent to injections in that joint. It is also contemplated that embodiments of the present invention may be useful for injection or administration into soft tissues or lesions. Any and all uses of specific words and references are simply to detail different embodiments of the present invention.

Local administration of a corticosteroid microparticle formulation can occur, for example, by injection into the intra-articular space, peri-articular space, soft tissues, lesions, epidural space, perineural space, or the foraminal space at or near the site of a patient's pain and/or structural tissue damage. Local injection of the formulations described herein into articular or periarticular spaces may be useful in the treatment of, for example, juvenile rheumatoid arthritis, sciatica and other forms of radicular pain (e.g., arm, neck, lumbar, thorax), psoriatic arthritis, acute gouty arthritis, Morton's neuroma, acute and subacute bursitis, acute and subacute nonspecific tenosynovitis and epicondylitis, acute rheumatic carditis and ankylosing spondylitis. Injection of the microparticles described herein into soft tissues or lesions may be useful in the treatment of, for example, alopecia areata, discoid lupus, erythematous; keloids, localized hypertrophic, infiltrated inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), psoriasis and psoriatic plaques; necrobiosis lipoidica diabetorum, and psoriatic arthritis. Injection of the microparticles described herein into epidural spaces may be useful in the treatment of, for example, neurogenic claudication. Intramuscular or other soft tissues or lesions injections may also be useful in providing systemic exposures that are effective in the control of incapacitating allergic conditions (including but not limited

to asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, seasonal or perennial allergic rhinitis, serum sickness, transfusion reactions), bullous dermatitis herpetiformis, exfoliative dermatitis, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome), Primary or secondary adrenocortical insufficiency in conjunction with mineralocorticoids where applicable; congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsupportive thyroiditis, exacerbations of regional enteritis and ulcerative colitis, acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond blackfan anemia), pure red cell aplasia, select cases of secondary thrombocytopenia, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy, palliative management of leukemias and lymphomas, acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor or craniotomy, to induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, or to induce diuresis or remission of proteinuria in lupus erythematosus, berylliosis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis (when used concurrently with appropriate antituberculous chemotherapy), idiopathic eosinophilic pneumonias, symptomatic sarcoidosis, dermatomyositis, polymyositis, and systemic lupus erythematosus, post-operative pain and swelling.

In one embodiment, the corticosteroid microparticle formulations provided herein are useful in treating, alleviating a symptom of, ameliorating and/or delaying the progression of sciatica. In one embodiment, corticosteroid microparticle formulations provided herein are useful in treating, alleviating a symptom of, ameliorating and/or delaying the progression of temporomandibular joint disorder (TMD).

In one embodiment, the corticosteroid microparticle formulations provided herein are useful in treating, alleviating a symptom of, ameliorating and/or delaying the progression of neurogenic claudication secondary to lumbar spinal stenosis (LSS). LSS implies spinal canal narrowing with possible subsequent neural compression (classified by anatomy or etiology). Neurogenic Claudication (NC) is a hallmark symptom of lumbar stenosis, in which the column of the spinal cord (or the canals that protect the nerve roots) narrows at the lower back. This narrowing can also occur in the spaces between the vertebrae where the nerves leave the spine to travel to other parts of the body.

The microparticles of the invention are used to treat, alleviate a symptom of, ameliorate and/or delay the progression patients suffering from NC secondary to LSS. The corticosteroid microparticle formulations can be administered, for example, by epidural steroid injection (ESI).

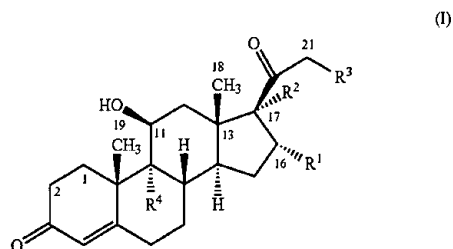
Administration of a corticosteroid microparticle formulation, e.g., a TCA microparticle formulation, to a patient suffering from an inflammatory disease such as osteoarthritis or rheumatoid arthritis, is considered successful if any of a variety of laboratory or clinical results is achieved. For example, administration of a corticosteroid microparticle formulation is considered successful if one or more of the symptoms associated with the disease is alleviated, reduced, inhibited or does not progress to a further, i.e., worse, state. Administration of a corticosteroid microparticle formulation is considered successful if the disease, e.g., an arthritic or other inflammatory disease, enters remission or does not progress to a further, i.e., worse, state.

Also, any and all alterations and further modifications of the invention, as would occur to one of ordinary skill in the art, are intended to be within the scope of the invention

Selection of Corticosteroids and Drug Dosage

Corticosteroids associated with embodiments of the present invention can be any naturally occurring or synthetic steroid hormone. Naturally occurring corticosteroids are secreted by the adrenal cortex or generally the human body.

Corticosteroid molecules have the following basic structure:



Corticosteroids have been classified into four different groups (A, B, C, and D). (See e.g., Foti et al. "Contact Allergy to Topical Corticosteroids: Update and Review on Cross-Sensitization." *Recent Patents on Inflammation & Allergy Drug Discovery* 3 (2009): 33-39; Coopman et al., "Identification of cross-reaction patterns in allergic contact dermatitis to topical corticosteroids." *Br J Dermatol* 121 (1989): 27-34). Class A corticosteroids are hydrocortisone types with no modification of the D ring or C20-C21 or short chain esters on C20-C21. Main examples of Class A corticosteroids include prednisolone, hydrocortisone and methylprednisolone and their ester acetate, sodium phosphate and succinate, cortisone, prednisone, and tixocortol pivalate. Class B corticosteroids are triamcinolone acetonide (TCA) types with cis/ketalic or diolic modifications on C16-C17. Main examples of Class B corticosteroids include triamcinolone acetonide (TCA), fluocinolone acetonide, amcinonide, desonide, fluocinonide, halcinonide, budesonide, and flunisolide. Class C corticosteroids are betamethasone types with a —CH₃ mutation on C16, but no esterification on C17-C21. Main examples of Class C corticosteroids include betamethasone, dexamethasone, desoxymethasone, flucortolone, and halomethasone. Class D corticosteroids are clobetasone or hydrocortisone esterified types with a long chain on C17 and/or C21 and with no methyl group on C16. Main examples of Class D corticosteroids include fluticasone, clobetasone butyrate, clobetasol propionate, hydrocortisone-17-aceponate, hydrocortisone-17-butyrate, beclomethasone dipropionate, betamethasone-17-valerate, betamethasone dipropionate, methylprednisolone aceponate, and prednicarbate.

For the present invention non-limiting examples of corticosteroids may include: betamethasone, betamethasone acetate, betamethasone dipropionate, betamethasone 17-valerate, cortivazol, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, hydrocortisone, hydrocortisone aceponate, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone cypionate, hydrocortisone probutate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydrocortisone valerate, methylprednisolone, methylprednisolone aceponate, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone metasulphobenzoate, prednisolone sodium phosphate, prednisolone steaglate,

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prednisolone tebutate, triamcinolone, triamcinolone acetonide, triamcinolone acetonide 21-palmitate, triamcinolone benetonide, triamcinolone diacetate, triamcinolone hexacetonide, alclometasone, alclometasone dipropionate, amcinonide, amelometasone, beclomethasone, beclomethasone dipropionate, beclomethasone dipropionate monohydrate, budesonide, butixocort, butixocort propionate, ciclesonide, ciprocinonide, clobetasol, clobetasol propionate, clocortolone, clobetasone, clobetasone butyrate, clocortolone pivalate, cloprednol, cortisone, cortisone acetate, deflazacort, domoprednate, deprodone, deprodone propionate, desonide, desoximethasone, desoxycortone, desoxycortone acetate, dichlorisone, diflorasone, diflorasone diacetate, diflucortolone, difluprednate, flucorolone, flucorolone acetonide, fludrocortisone, fludrocortisone acetate, fludroxycortide, flumethasone, flumethasone pivalate, flunisolide, fluocinolone, fluocinolone acetonide, flucortin, flucortolone, fluorometholone, fluticasone, fluticasone furoate, fluticasone propionate, fluorometholone acetate, fluoxymesterone, fluperolone, fluprednidene, fluprednidene acetate, fluprednisolone, formocortol, halcinonide, halobetasol propionate, halometasone, halopredone, halopredone acetate, hydrocortamate, isoflupredone, isoflupredone acetate, itrocinonide, loteprednol etabonate, mazipredone, meclorisone, meclorisone dibutyrate, medrysone, meprednisone, mometasone, mometasone furoate, mometasone furoate monohydrate, nivacortol, paramethasone, paramethasone acetate, prednazoline, prednicarbate, prednisolone, prednylidene, procinonide, rofleponide, rimexolone, timobesone, tipredane, tixocortol, tixocortol pivalate and tralonide.

Embodiments of the invention include using sustained release corticosteroids delivered to treat pain at dosages that do not adversely suppress the HPA axis. Such amounts delivered locally to relieve pain due to inflammation, will provide a systemic concentration that does not have a measurable adverse effect on the HPA axis (differences if any are not significant because any such differences are within normal assay variability) or, as desired, may have a measurable but clinically insignificant effect on the HPA axis (basal cortisol is suppressed to some measurable extent but stress responses are adequately preserved). Further embodiments of the invention include doses during a second period of time selected to adjust for a change in sensitivity of the HPA axis to suppression following exposure during a first period of time to the corticosteroid (FIG. 1).

Additional embodiments include doses during first and/or the second period of time selected to adjust for corticosteroid-specific (or corticosteroid- and potentially dose-specific) changes in the rate of change of sensitivity of the HPA axis to suppression that begin with initial exposure. For clinically effective corticosteroids, the rate of change of the sensitivity of the HPA axis to exogenous corticosteroids is both non-uniform and non-linear (FIG. 2). The rate and pattern of change in such sensitivity varies widely as a function of the particular corticosteroid that is selected (FIG. 3).

Finally, it is possible to usefully characterize the change in sensitivity vs. time mathematically as the (non-linear, exponential) "decay" of the sensitivity from the initial to final value, wherein the decay parameters (Table 1) has been determined from the data further described herein.

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TABLE 1

HPA Axis Change-in-Sensitivity Decay-Parameter δ vs. Corticosteroid and Dose *	
Corticosteroid	Decay Parameter δ (time ⁻¹)
Betamethasone Phosphate/Acetate (7 mg)	0.024
Triamcinolone Acetonide (40 mg)	0.005
Triamcinolone Hexacetonide (20 mg)	0.070

* The inhibition of endogenous cortisol synthesis can be related to the exogenous corticosteroid concentration by the following equations:
1. $E = (E_{max} \cdot C^n) / (EC_{50}^n + C^n)$ wherein E = effect, E_{max} = maximal effect, C = concentration of exogenous corticosteroid, EC_{50} = concentration at 1/2 E_{max} , and n = the Hill ("shape", or "slope") factor; and
2. $EC_{50-final} = EC_{50-initial} + [EC_{50-final} - EC_{50-initial}] \cdot [1 - e^{(-\delta \cdot time)}]$

Using this approach permits the determination of "δ", the parameter describing the exponential decay from the initial to the final EC_{50} . Minimization of least-squares differences was utilized to obtain the best-fit δ.

These new findings regarding the rate and pattern of change of sensitivity to inhibition and the lack of predictability of such rates and patterns on the basis of, for example, steroid potency, have significant implications for clinically appropriate dose-selection. Those skilled in the art will appreciate the importance of a changing sensitivity to HPA axis suppression and will also appreciate both the complexity and counterintuitive aspects of several of these new findings (Table 1).

As a result of these clinical findings, the dose range to achieve clinically useful analgesia, with minimal or controlled modulation of the HPA axis, at steady state concentrations of various corticosteroids has been determined (Table 2). In particular, it appears that the daily corticosteroid doses at steady state concentrations, are approximately 3- to 7-times greater than are predicted by prior art (Meibohm, 1999).

TABLE 2

Dose (mg/d), adjusted for individual intra-articular corticosteroid characteristics, for expected suppression of endogenous cortisol production at steady state.					
Corticosteroid	Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
betamethasone (mg/d)	0.1	0.2	0.5	1.0	1.8
budesonide (mg/d)	0.1	0.2	0.6	1.2	2.2
des-ciclesonide (mg/d)	3.0	6.3	14.3	30.7	57.0
dexamethasone (mg/d)	0.1	0.2	0.4	0.9	1.6
flunisolide (mg/d)	0.3	0.5	1.2	2.6	4.8
fluticasone (mg/d)	0.1	0.1	0.3	0.6	1.1
mometasone (mg/d)	0.2	0.4	0.9	2.0	3.7
methylprednisolone (mg/d)	0.3	0.7	1.6	3.5	6.5
prednisolone (mg/d)	0.4	0.8	1.9	4.0	7.5
triamcinolone acetonide (mg/d)	0.2	0.4	0.8	1.7	3.2
triamcinolone hexacetonide (mg/d)	0.1	0.2	0.4	0.9	1.6

TABLE 2A

Total Dose Delivered (mg/month), adjusted for individual intra-articular corticosteroid characteristics, for expected suppression of endogenous cortisol production at steady state.					
Corticosteroid	Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
betamethasone	3.0	6.0	15.0	30.0	54.0
budesonide	3.0	6.0	18.0	36.0	66.0

TABLE 2A-continued

Total Dose Delivered (mg/month), adjusted for individual intra-articular corticosteroid characteristics, for expected suppression of endogenous cortisol production at steady state.					
Corticosteroid	Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
des-ciclesonide	90.0	189.0	429.0	921.0	1710.0
dexamethasone	3.0	6.0	12.0	27.0	48.0
flunisonide	9.0	15.0	36.0	78.0	144.0
fluticasone	3.0	3.0	9.0	18.0	33.0
mometasone	6.0	12.0	27.0	60.0	111.0
methylprednisolone	9.0	21.0	48.0	105.0	195.0
prednisolone	12.0	24.0	57.0	120.0	225.0
triamcinolone acetonide	6.0	12.0	24.0	51.0	96.0
triamcinolone hexacetonide	3.0	6.0	12.0	27.0	48.0

That higher doses of corticosteroids can be administered successfully by intra-articular injection, maximizing the likelihood of observing anti-inflammatory and analgesic responses while minimizing or eliminating adverse events from HPA axis suppression or otherwise excessive tissue exposure, is of profound clinical consequence for improving the treatment of patients with arthritis.

In addition, with these continuous daily doses of intra-articular corticosteroids, it is possible to determine the related systemic plasma level concentrations (Table 3) that will produce the target cortisol inhibition and not beyond, this while retaining clinically important anti-inflammatory and analgesic activity within the joint. These plasma concentrations were predicted on the basis of data from short term (i.e., less than 8 days) exposure to corticosteroids. With longer exposure to corticosteroids, the "decay" (i.e., decline) of the sensitivity to corticosteroids may continue resulting in values higher than those listed in Table 3. The levels calculated in Table 3 were purely hypothetical calculations based on human data with immediate release-level doses from the literature. With sustained release dosages, more drug may be able to be delivered without seeing an increased level of cortisol inhibition after the initial burst period. A given level of plasma concentration may actually provide less inhibition that would have been predicted or calculated using the human IR levels from the literature.

TABLE 3

Plasma corticosteroid concentrations associated with target levels of cortisol inhibition at steady state.					
Corticosteroid	Corticosteroid Concentration in Plasma (ng/mL) associated with the Target Levels of Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
betamethasone (ng/mL)	0.33	0.70	1.57	3.38	6.27
budesonide (ng/mL)	0.60	1.27	2.85	6.14	11.40
des-ciclesonide (ng/mL)	0.55	1.16	2.61	5.63	10.45
dexamethasone (ng/mL)	0.21	0.44	1.00	2.15	3.99
flunisonide (ng/mL)	0.18	0.38	0.86	1.84	3.42
fluticasone (ng/mL)	0.04	0.08	0.19	0.41	0.76
mometasone (ng/mL)	0.15	0.32	0.71	1.54	2.85
methylprednisolone (ng/mL)	0.68	1.44	3.23	6.96	12.92
prednisolone (ng/mL)	1.64	3.46	7.79	16.79	31.16
triamcinolone acetonide (ng/mL)	0.19	0.40	0.90	1.95	3.61
triamcinolone hexacetonide (ng/mL)	0.10	0.21	0.48	1.02	1.90

The studies presented herein demonstrate for the first time the discovery of the time-course of changes in sensitivity of

the HPA axis to exogenous corticosteroids. In addition, both the mean doses and mean plasma levels shown in Tables 2 and 3 above are those after steady state has been achieved, requiring approximately 4 to 24 days depending upon the corticosteroid in question. The companion post-dose but pre-steady-state transients for several corticosteroids have been described in FIGS. 2, 3, and 4. It is also important to note that the data suggest that the carefully controlled benefits from the intra-articular, sustained release of a corticosteroid of interest will persist as long as release continues.

In one preferred embodiment, a single component sustained release formulation releases a dose (in mg/day) that suppresses the HPA axis by no more than between 5-40% at steady state as shown in Table 2, more preferably no more than between 10-35% at steady state as shown in Table 2. These doses are therapeutically effective without adverse side effects.

In another preferred embodiment, a single component sustained release formulation releases a dose (in mg/day) that does not measurably suppress the HPA axis at steady state. These doses are therapeutically effective without adverse side effects.

In another embodiment where both an immediate release component and sustained release component of the formulation are present, immediate release dose would be as shown in Table 4 and the sustained release dose would be a dose (in mg/day) that suppresses the HPA axis by no more than between 5-40% as shown in Table 2, more preferably no more than between 10-35% as shown in Table 2. In addition, it is expected that sustained release doses described previously will follow immediate release doses as shown in Table 4.

TABLE 4

Immediate release relative doses (mg)	
Corticosteroid	Immediate Release Dose (mg)
betamethasone ¹	5-20
budesonide ²	7-28
des-ciclesonide ²	177-713
dexamethasone ²	5-20
flunisonide ²	15-60
fluticasone ²	3-12
mometasone ²	11-44
methylprednisolone ¹	40-160
prednisolone ¹	25-100
triamcinolone acetonide ¹	10-40
triamcinolone hexacetonide ¹	10-40

¹clinical doses
²calculated doses

Sustained Release Delivery Platforms

The manufacture of microparticles or methods of making biodegradable polymer microparticles are known in the art. Microparticles from any of the biodegradable polymers listed below can be made by, but not limited to, spray drying, solvent evaporation, phase separation, spray drying, fluidized bed coating or combinations thereof.

In certain embodiments of the invention, the microparticles are made from a biodegradable polymer that may include, without limitation, natural or synthetic biocompatible biodegradable materials. Natural polymers include, but are not limited to, proteins such as albumin, collagen, gelatin synthetic poly(aminoacids), and prolamines; glycosaminoglycans, such as hyaluronic acid and heparin; polysaccharides, such as alginates, chitosan, starch, and dextrans; and other naturally occurring or chemically modified biodegradable polymers. Synthetic biocompatible biodegradable materials

include, but are not limited to the group comprising of, poly (lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PG), polyhydroxybutyric acid, poly(trimethylene carbonate), polycaprolactone (PCL), polyvalerolactone, poly (alpha-hydroxy acids), poly(lactones), poly(amino-acids), poly(anhydrides), polyketals poly(arylates), poly(orthoesters), poly(orthocarbonates), poly(phosphoesters), poly(ester-co-amide), poly(lactide-co-urethane, polyethylene glycol (PEG), polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer(polyactive), polyurethanes, polythioesters, methacrylates, poly(N-isopropylacrylamide), PEO-PPO-PEO (pluronic), PEO-PPO-PAA copolymers, and PLGA-PEO-PLGA blends and copolymers thereof, multi-block polymer configurations such as PLGA-PEG-PLGA, and any combinations thereof. These polymers may be used in making controlled release or sustained release compositions disclosed herein.

In a preferred embodiment, the microparticles are formed from poly(D,L-lactic-co-glycolic acid) (PLGA), which is commercially available from a number of sources. Biodegradable PLGA copolymers are available in a wide range of molecular weights and ratios of lactic to glycolic acid. If not purchased from a supplier, then the biodegradable PLGA copolymers may be prepared by the procedure set forth in U.S. Pat. No. 4,293,539 (Ludwig, et al.), the disclosure of which is hereby incorporated by reference in its entirety. Ludwig prepares such copolymers by condensation of lactic acid and glycolic acid in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). However, any suitable method known in the art of making the polymer can be used.

In the coacervation process, a suitable biodegradable polymer is dissolved in an organic solvent. Suitable organic solvents for the polymeric materials include, but are not limited to acetone, halogenated hydrocarbons such as chloroform and methylene chloride, aromatic hydrocarbons such as toluene, halogenated aromatic hydrocarbons such as chlorobenzene, and cyclic ethers such as dioxane. The organic solvent containing a suitable biodegradable polymer is then mixed with a non-solvent such as silicone based solvent. By mixing the miscible non-solvent in the organic solvent, the polymer precipitates out of solution in the form of liquid droplets. The liquid droplets are then mixed with another non-solvent, such as heptane or petroleum ether, to form the hardened microparticles. The microparticles are then collected and dried. Process parameters such as solvent and non-solvent selections, polymer/solvent ratio, temperatures, stirring speed and drying cycles are adjusted to achieve the desired particle size, surface smoothness, and narrow particle size distribution.

In the phase separation or phase inversion procedures entrap dispersed agents in the polymer to prepare microparticles. Phase separation is similar to coacervation of a biodegradable polymer. By addition of a nonsolvent such as petroleum ether, to the organic solvent containing a suitable biodegradable polymer, the polymer is precipitates from the organic solvent to form microparticles.

In the salting out process, a suitable biodegradable polymer is dissolved in an aqueous miscible organic solvent. Suitable water miscible organic solvents for the polymeric materials include, but are not limited to acetone, as acetone, acetonitrile, and tetrahydrofuran. The water miscible organic solvent containing a suitable biodegradable polymer is then mixed with an aqueous solution containing salt. Suitable salts include, but are not limited to electrolytes such as magnesium chloride, calcium chloride, or magnesium acetate and non-electrolytes such as sucrose. The polymer precipitates from the organic solvent to form microparticles, which are col-

lected and dried. Process parameters such as solvent and salt selection, polymer/solvent ratio, temperatures, stirring speed and drying cycles are adjusted to achieve the desired particle size, surface smoothness, and narrow particle size distribution.

Alternatively, the microparticles may be prepared by the process of Ramstack et al., 1995, described in published international patent application WO 95/13799, the disclosure of which is incorporated herein in its entirety. The Ramstack et al. process essentially provides for a first phase, including an active agent and a polymer, and a second phase, that are pumped through a static mixer into a quench liquid to form microparticles containing the active agent. The first and second phases can optionally be substantially immiscible and the second phase is preferably free from solvents for the polymer and the active agent and includes an aqueous solution of an emulsifier.

In the spray drying process, a suitable biodegradable polymer is dissolved in an organic solvent and then sprayed through nozzles into a drying environment provided with sufficient elevated temperature and/or flowing air to effectively extract the solvent. Adding surfactants, such as sodium lauryl sulfate can improve the surface smoothness of the microparticles.

Alternatively, a suitable biodegradable polymer can be dissolved or dispersed in supercritical fluid, such as carbon dioxide. The polymer is either dissolved in a suitable organic solvent, such as methylene chloride, prior to mixing in a suitable supercritical fluid or directly mixed in the supercritical fluid and then sprayed through a nozzle. Process parameters such as spray rate, nozzle diameter, polymer/solvent ratio, and temperatures, are adjusted to achieve the desired particle size, surface smoothness, and narrow particle size distribution.

In a fluidized bed coating, the drug is dissolved in an organic solvent along with the polymer. The solution is then processed, e.g., through a Wurster air suspension coating apparatus to form the final microcapsule product.

The microparticles can be prepared in a size distribution range suitable for local infiltration or injection. The diameter and shape of the microparticles can be manipulated to modify the release characteristics. In addition, other particle shapes, such as, for example, cylindrical shapes, can also modify release rates of a sustained release corticosteroid by virtue of the increased ratio of surface area to mass inherent to such alternative geometrical shapes, relative to a spherical shape. The microparticles have a mass mean diameter ranging between about 0.5 to 500 microns. In a preferred embodiment, the microparticles have a mass mean diameter of between 10 to about 100 microns.

Biodegradable polymer microparticles that deliver sustained release corticosteroids may be suspended in suitable aqueous or non-aqueous carriers which may include, but is not limited to water, saline, pharmaceutically acceptable oils, low melting waxes, fats, lipids, liposomes and any other pharmaceutically acceptable substance that is lipophilic, substantially insoluble in water, and is biodegradable and/or eliminatable by natural processes of a patient's body. Oils of plants such as vegetables and seeds are included. Examples include oils made from corn, sesame, cannoli, soybean, castor, peanut, olive, arachis, maize, almond, flax, safflower, sunflower, rape, coconut, palm, babassu, and cottonseed oil; waxes such as carnoba wax, beeswax, and tallow; fats such as triglycerides, lipids such as fatty acids and esters, and liposomes such as red cell ghosts and phospholipid layers.

Corticosteroid Loading of and Release from Biodegradable Polymer Microparticles

When an intra-articularly delivered corticosteroid is incorporated into a biodegradable polymer for sustained release into a joint at a dosage that does not suppress the HPA axis, preferred loadings of said corticosteroid are from about 5% to about 40% (w/w) of the polymer, preferably about 5% to about 30%, more preferably about 5% to about 28% of the polymer.

As the biodegradable polymers undergo gradual bio-erosion within the joint, the corticosteroid is released to the inflammatory site. The pharmacokinetic release profile of the corticosteroid by the biodegradable polymer may be first order, zero order, bi- or multi-phasic, to provide desired treatment of inflammatory related pain. In any pharmacokinetic event, the bio-erosion of the polymer and subsequent release of the corticosteroid may result in a controlled release of a corticosteroid from the polymer matrix. The rate of release at dosages that do not suppress the HPA axis are described above.

Excipients

The release rate of the corticosteroid from a biodegradable polymer matrix can be modulated or stabilized by adding a pharmaceutically acceptable excipient to the formulation. An excipient may include any useful ingredient added to the biodegradable polymer depot that is not a corticosteroid or a biodegradable polymer. Pharmaceutically acceptable excipients may include without limitation lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, PEG, polysorbate 20, polysorbate 80, polyvinylpyrrolidone, cellulose, water, saline, syrup, methyl cellulose, and carboxymethyl cellulose. An excipient for modulating the release rate of a corticosteroid from the biodegradable drug depot may also include without limitation pore formers, pH modifiers, reducing agents, antioxidants, and free radical scavengers.

Delivery of Corticosteroid Microparticles

Parenteral administration of formulations of the invention can be effected by intra-articular injection or other injection using a needle. To inject the microparticles into a joint, needles having a gauge of about 14-28 gauge are suitable. It will be appreciated by those skilled in the art that formulations of the present invention may be delivered to a treatment site by other conventional methods, including catheters, infusion pumps, pens devices, injection guns and the like.

All references, patents, patent applications or other documents cited are hereby incorporated by reference.

EXAMPLES

The present invention is further defined in the following Examples. It should be understood that these Examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these Examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.

Example 1

Sustained-Release Betamethasone or Triamcinolone Acetonide Microparticles

In one embodiment, the microparticle formulation contains a copolymer of DL-lactide (or L-lactide) and glycolide

in a 45:55 molar ratio (up to 75:25 molar ratio) with an inherent viscosity ranging from 0.15 to 0.60 dL/g with either an ester or acid end group plus either the corticosteroid betamethasone or triamcinolone acetonide. If betamethasone is used, then the betamethasone is in the form of either betamethasone acetate, betamethasone dipropionate or a combination thereof. The total amount of betamethasone or triamcinolone acetonide incorporated into the microparticle ranges from 10% to 30% (w/w). The microparticles are formulated to mean mass range in size from 10 to 100 microns. The population of microparticles is formulated to be delivered through a 19 gauge or higher needle. Additional excipients may be added such as, but not limited to, carboxymethylcellulose sodium, mannitol, polysorbate-80, sodium phosphate, sodium chloride, polyethylene glycol to achieve isotonicity and promote syringeability. If betamethasone is used, then the betamethasone incorporated into the microparticle population provides an initial release (burst) of about 5-20 mg of drug over a period of 1 to 12 hours, followed by a steady state release of drug at a rate of about 0.1 to 1.0 mg/day over a period of 14 to 90 days. If triamcinolone acetonide is used, then the drug incorporated into the microparticle population provides an initial release (burst) of about 10-40 mg of drug over a period of 1 to 12 hours, followed by a steady state release of drug at a rate of about 0.2 to 1.7 mg/day over a period of 14 to 90 days.

Example 2

Sustained-Release Betamethasone or Triamcinolone Acetonide Microparticles with an Immediate Release Form

In another embodiment, the microparticle formulation of Example 1 is further admixed with an immediate release betamethasone or triamcinolone acetonide component, such as a betamethasone or triamcinolone acetonide containing solution. If betamethasone is used, then the betamethasone in the immediate release component is in the form of either betamethasone acetate, betamethasone dipropionate or a combination thereof. If betamethasone is used, then the immediate release component provides an initial release of a total of about 5 to 20 mg of betamethasone over the first 1-10 days, while the sustained release component releases betamethasone at a rate of about 0.1 to 1.0 mg/day over the first 14 to 90 days following administration. If triamcinolone acetonide is used, then the immediate release component provides an initial release of a total of 10 to 40 mg of drug over the first 1-10 days, while the sustained release component releases drug at a rate of about 0.2 to 1.7 mg/day over the first 14 to 90 days following administration.

Example 3

Determination of Time-Variance in HPA Axis Sensitivity

Adult volunteers (N=4 to 9 per group) give appropriate informed consent. Each individual in each group receives a single intra-articular administration of an exogenous corticosteroid (triamcinolone acetonide 40 mg; triamcinolone hexacetonide 20; betamethasone 7 mg (disodium phosphate 4 mg/acetate 3 mg). Blood samples for measurement of corticosteroid concentrations and/or cortisol concentrations are drawn at 8 AM at baseline and on days 1, 7, 9, 10, 12, 14, 18, and 21. The extent of suppression of endogenous cortisol was measured in each subject in each group. The extent of cortisol

suppression predicted by previously published models (Meibohm, 1999) was determined and compared to observations (FIG. 4 Column 1). The change (decrease) in HPA axis sensitivity vs. time is then determined on a day-by-day and final basis (FIG. 4, Column 2), permitting determination of the correct steady-state intra-articular doses of corticosteroid to achieve, or limit, HPA axis suppression to the desired level.

Example 4

Preparation of Triamcinolone Acetonide Microparticles by Spinning Disk

A pharmaceutical depot was prepared comprised of the corticosteroid, triamcinolone acetonide (TCA, 9α-Fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-acetonide; 9α-Fluoro-16α-hydroxyprednisolone 16α, 17α-acetonide) incorporated into PLGA microparticles.

In one suitable thirty day formulation, 250 mg of triamcinolone acetonide and 750 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.4 dL/g and molecular weight of 54 kDa) were dispersed in 14.25 grams of dichloromethane. The dispersion was atomized into micro-droplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 μm sieve.

Particle size of the TCA incorporated microparticles was determined using laser diffraction (Malvern Mastersizer 2000) by dispersing a 250 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. Sonication was maintained as the sample was stirred at 2500 rpm and measurements taken every 15 seconds, with the average of three measurements reported. 10 mg of TCA containing microparticles were added to 10 mL of dimethylsulfoxide (DMSO), mixed until dissolved and an aliquot analyzed by HPLC to determine the microparticle drug load. Another 4 mg of TCA containing microparticles were suspended in 20 mL of phosphate buffered saline (PBS) containing 0.5% sodium dodecyl sulfate (SDS) maintained at 37° C. 0.5 mL of the media was removed at regular intervals, replaced at each interval with an equivalent amount of fresh media to maintain a constant volume, and analyzed by HPLC to determine microparticle in vitro release. Analysis by HPLC was conducted using a C18 (Waters Nova-Pack C-18, 3.9×150 mm) and 35% acetonitrile mobile phase at 1 mL/min flow rate with UV detection at 240 nm. The results are shown in Table 5.

TABLE 5

Analytical Results for 25% Triamcinolone Acetonide PLGA 75:25 Microparticles				
PLGA(lactide: glycolide molar ratio/ inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
75:25	24	96	D0.1: 32 μm	0.2 day: 5.1
carboxylic acid end-capped			D0.5: 49 μm	1 day: 13.5
0.4 dL/g			D0.9: 73 μm	3 day: 29.6
				7 day: 52.6

TABLE 5-continued

Analytical Results for 25% Triamcinolone Acetonide PLGA 75:25 Microparticles				
PLGA(lactide: glycolide molar ratio/ inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
54 kDa				14 day 70.9
25%				21 day: 76.4
				28 day: 79.1

The in vitro cumulative release profile is graphed in FIG. 5.

In one iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would achieve a transient suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35% as shown in FIG. 6. In a second iteration of these data, the amount of triamcinolone acetonide released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35% as shown in FIG. 7. These calculated doses equal 376 mg of microparticles containing 94 mg of TCA and 80 mg of microparticles containing 20 mg of TCA, respectively.

In a second preparation of the same formulation, analyzed and in vitro release plotted in the same manner, the results are equivalent as shown in Table 6, and FIGS. 8, 9 and 10. The calculated human dose, as exemplified in Table 2 that would achieve a transient suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35% equals 280 mg of microparticles containing 70 mg of TCA. The calculated human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35% equals 68 mg of microparticles containing 17 mg of TCA.

TABLE 6

Analytical Results for Alternate Preparation of a Nominal 25% Triamcinolone Acetonide PLGA 75:25 Microparticles				
PLGA(lactide: glycolide molar ratio/ inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
75:25	27.5	110	D0.1: 30.9 μm	0.2 day: 4.8
carboxylic acid end-capped			D0.5: 48.2 μm	1 day: 15
0.4 dL/g			D0.9: 71.0 μm	3 day: 28.5
54 kDa				7 day: 50.2
25%				14 day 67.1
				21 day: 74.2
				28 day: 75.7

Influence of PEG on PLGA 75:25 Formulations

In other suitable formulations, polyethylene glycol was added to the PLGA 75:25 polymers while keeping the target amount of triamcinolone acetonide constant. PEG/PLGA blends are known to allow for more complete and faster release of pharmaceutical agents incorporated into microparticles than PLGA alone (Cleek et al. "Microparticles of poly

(DL-lactic-coglycolic acid)/poly(ethylene glycol) blends for controlled drug delivery." *J Control Release* 48 (1997): 259-268; Morlock, et al. "Erythropoietin loaded microspheres prepared from biodegradable LPLG-PEO-LPLG triblock copolymers: protein stabilization and in-vitro release properties." *J Control Release*, 56 (1-3) (1998): 105-115; Yeh, "The stability of insulin in biodegradable microparticles based on blends of lactide polymers and polyethylene glycol." *J Microencapsul*, 17(6) (2000): 743-56).

In one iteration, 250 mg of triamcinolone acetonide, 50 mg of polyethylene glycol (PEG 1450) and 700 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.4 dL/g and molecular weight of 54 kDa) were dispersed in 14 grams of dichloromethane. In another iteration, 250 mg of triamcinolone acetonide, 100 mg of polyethylene glycol (PEG 3350) and 650 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.4 dL/g and molecular weight of 54 kDa) were dispersed in 13 grams of dichloromethane. The dispersions were atomized into micro-droplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 µm sieve.

The microparticles were analyzed as described above and the data is shown in Table 7.

TABLE 7

Analytical Results of Nominal 25% Triamcinolone Acetonide PLGA 75:25 Microparticles containing Polyethylene Glycol (PEG) Additive				
PLGA(lactide: glycolide molar ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% TCA by weight)	Incor-poration effi-ciency (%)	Particle size (Dv, µm)	In vitro release (%)
75:25	29.4	118	D0.1: 36.2 µm	0.2 day: 3.6
carboxylic acid end-capped			D0.5: 59.0 µm	1 day: 13.8
0.4 dL/g			D0.9: 95.5 µm	3 day: 30.1
54 kDa				7 day: 49.5
25%				14 day: 65.5
5% PEG 1450				21 day: 74.0
75:25				28 day: 78.5
carboxylic acid end-capped	24.5	98	D0.1: 32.0 µm	0.2 day: 4.1
0.4 dL/g			D0.5: 52.4 µm	1 day: 11.7
54 kDa			D0.9: 79.0 µm	3 day: 24.5
25%				7 day: 40.8
10% PEG 3350				14 day: 55.8
				21 day: 63.7
				28 day: 69.5

The in vitro cumulative release profile is graphed in FIG. 11 and FIG. 12. PEG did not seem to enhance the release of the TCA in either formulation, as would be expected. In fact, at higher percentages of PEG, albeit a different molecular weight (higher percentages of PEG 1350 were unmanageable due to the agglomeration of microparticles), the release rate was slower.

In one iteration of these in vitro release data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35% as shown in FIG. 13 and FIG. 14. These calculated doses equal 296 mg of microparticles containing 74 mg of TCA and 316 mg of microparticles contain-

ing 79 mg of TCA, respectively. In a second iteration of these data, the amount of triamcinolone acetonide released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35% as shown in FIGS. 15 and 16. These calculated doses equal 68 mg of microparticles containing 17 mg of TCA and 88 mg of microparticles containing 22 mg of TCA, respectively.

Other TCA containing formulations were tried with PEG and PLGA 75:25 without success. A PLGA microparticle formulation containing 25% TCA and 25% PEG 1450 agglomerated during manufacture and storage. Another PLGA formulation containing 40% TCA and 15% PEG 1450 gave similar results to the microparticles containing 40% TCA and no PEG.

Influence of Triamcinolone Acetonide Content in PLGA 75:25 Microparticles:

Triamcinolone acetonide containing microparticle depots were prepared and analyzed, as described above, with the exception of using 100 mg, 150 mg, 200 mg and 400 mg triamcinolone acetonide and adding to a 5% PLGA dichloromethane solution. The physical characteristics of these formulations are shown in Table 8.

TABLE 8

Analytical Results of PLGA 75:25 Microparticles containing varying amounts of Triamcinolone Acetonide					
PLGA(lactide: glycolide molar ratio/inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incor-poration effi-ciency (%)	Particle size (Dv, µm)	In vitro release (%)	
75:25	43.4	109	D0.1: 40.7 µm	0.2 day: 6.6	
carboxylic acid end-capped			D0.5: 70.7 µm	1 day: 24.2	
0.4 dL/g			D0.9: 167 µm	3 day: 53.8	
54 kDa				7 day: 82.5	
40%				14 day: 89.4	
				21 day: 89.6	
				28 day: 87.5	
75:25	20.2	101	D0.1: 28.7 µm	0.2 day: 5.3	
carboxylic acid end-capped			D0.5: 45.2 µm	1 day: 13.5	
0.4 dL/g			D0.9: 70.5 µm	3 day: 23.7	
54 kDa				7 day: 35.3	
20%				14 day: 44.4	
				21 day: 48.1	
				28 day: 50.6	
75:25	15.9	106	D0.1: 30.7 µm	0.2 day: 3.9	
carboxylic acid end-capped			D0.5: 47.8 µm	1 day: 9.0	
0.4 dL/g			D0.9: 74.8 µm	3 day: 14.2	
54 kDa				7 day: 19.3	
15%				14 day: 22.7	
				21 day: 24.6	
				28 day: 27.6	
75:25	11.7	117	D0.1: 31.0 µm	0.2 day: 2.3	
carboxylic acid end-capped			D0.5: 57.9 µm	1 day: 4.4	
0.4 dL/g			D0.9: 118 µm	3 day: 5.9	
54 kDa				7 day: 7.5	
10%				14 day: 9.9	
				21 day: 11.7	
				28 day: 15.8	

The in vitro cumulative release profiles for these four other TCA containing PLGA 75:25 microparticle depots are graphed in FIG. 17, along with the preferred formulation (25% TCA). The tabulated data and graph show the impact of the percent TCA incorporated in the PLGA microparticles on the in vitro release profile. The 10%, 15% and 20% TCA containing PLGA microparticles exhibit a slower release profile, with a significant less cumulative release over 28 days,

less than 20%, 30% and 55% respectively, than the 25% TCA PLGA depot exemplified in Example 4. The 40% TCA containing depot exhibits a faster release profile, with greater than 80% of the triamcinolone released by day 7 with a similar total cumulative release, than the 25% TCA PLGA depot exemplified in Example 4.

Influence of Molecular Weight on TCA PLGA 75:25 Microparticle Formulations:

In another microparticle formulation, triamcinolone acetonide was incorporated in PLGA of the same lactide to glycolide molar ratio as cited in Example 4 but of a lower molecular weight. Low molecular weight PLGA is known to allow for more complete and faster release of pharmaceutical agents incorporated into microparticles than their higher molecular weight counterparts. (Anderson et al. "Biodegradation and biocompatibility of PLA and PLGA microspheres." *Advanced Drug Delivery Reviews* 28 (1997): 5-24; Bouissou et al., "Poly(lactic-co-glycolic acid) Microspheres." *Polymer in Drug Delivery* (2006): Chapter 7).

250 mg of triamcinolone acetonide and 750 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.27 dL/g and molecular weight of 29 kDa) were dispersed in 14.25 grams of dichloromethane. The dispersion was atomized into micro-droplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 µm sieve.

Particle size of the TCA incorporated microparticles was determined using laser diffraction (Malvern Mastersizer 2000) by dispersing a 250 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. Sonication was maintained as the sample was stirred at 2500 rpm and measurements taken every 15 seconds, with the average of three measurements reported. 10 mg of TCA containing microparticles were added to 10 mL of dimethylsulfoxide (DMSO), mixed until dissolved and an aliquot analyzed by HPLC to determine the microparticle drug load. Another 4 mg of TCA containing microparticles were suspended in 20 mL of phosphate buffered saline (PBS) containing 0.5% sodium dodecyl sulfate (SDS) maintained at 37° C. 0.5 mL of the media was removed at regular intervals, replaced at each interval with an equivalent amount of fresh media to maintain a constant volume, and analyzed by HPLC to determine microparticle in vitro release. Analysis by HPLC was conducted using a C18 (Waters Nova-Pack C-18, 3.9x150 mm) and 35% acetonitrile mobile phase at 1 ml/min flow rate with UV detection at 240 nm. The results are shown in Table 9.

TABLE 9

Analytical Results of a Nominal 25% Triamcinolone Acetonide PLGA 75:25 (29 kDa) Microparticles					
PLGA(lactide: glycolide molar ratio/ inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (%) TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, µm)	In vitro release (%)	
75:25	29.4	118	D0.1: 34.1 µm	0.2 day: 4.0	
carboxylic			D0.5: 56.5 µm	1 day: 11.3	
acid end-capped			D0.9: 95.2 µm	3 day: 22.5	
0.27 dL/g				7 day: 35.9	

TABLE 9-continued

Analytical Results of a Nominal 25% Triamcinolone Acetonide PLGA 75:25 (29 kDa) Microparticles					
PLGA(lactide: glycolide molar ratio/ inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (%) TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, µm)	In vitro release (%)	
29 kDa				14 day: 48.3	
25%				21 day: 53.4	
				28 day: 56.5	

In vitro cumulative release data is graphed in FIG. 18, along with the preferred formulation using a higher molecular PLGA 75:25. The use of lower molecular weight PLGA (29 kDa) did not improve the release of the triamcinolone acetonide from the microparticles as expected, in fact the rate of release decreased and the release was incomplete as compared to higher molecular weight PLGA (PLGA, 54 kDa).

In another formulation of low molecular weight PLGA 75:25(29 kDa), polyethylene glycol, 10% PEG 3350, was added while maintaining the same amount of triamcinolone acetonide. As shown with other PEG containing formulations, there was no impact of this additive on the cumulative percent in vitro release profile as compared to the formulation not containing PEG (data not shown).

Influence of PLGA Lactide to Glycolide Ratio:

In other triamcinolone acetonide microparticle formulations, PLGA of equimolar lactide to glycolide ratio were employed instead of PLGA (75:25). PLGA (50:50) is known to allow for faster degradation and release of pharmaceutical agents incorporated into microparticles than PLGA's with greater lactide versus glycolide content (Anderson et al. "Biodegradation and biocompatibility of PLA and PLGA microspheres." *Advanced Drug Delivery Reviews* 28 (1997): 5-24; Bouissou et al., "Poly(lactic-co-glycolic acid) Microspheres." *Polymer in Drug Delivery* (2006): Chapter 7). Multiple formulations using PLGA 50:50 with differing amounts of triamcinolone acetonide, with and without PEG, different PLGA molecular weights and different PLGA endcaps were exemplified.

Formulations were prepared with 200 mg, 250 mg, 300 mg and 350 mg of triamcinolone acetonide and corresponding amount of PLGA (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.48 dL/g and molecular weight of 66 kDa) to yield 1000 mg total solids were dispersed into a quantity of dichloromethane to achieve a 5% PLGA solution. In another iteration, 300 mg of triamcinolone acetonide, 100 mg of polyethylene glycol (PEG 3350) and 650 mg of PLGA (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.48 dL/g and molecular weight of 66 kDa) were dispersed in 14.25 grams of dichloromethane. In another iteration, 300 mg of triamcinolone acetonide and 700 mg of PLGA (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.18 dL/g and molecular weight of 18 kDa) to yield 1000 mg total solids were dispersed in 14.25 grams of dichloromethane. The dispersions were atomized into micro-droplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 µm sieve.

Particle size of the TCA incorporated microparticles was determined using laser diffraction (Malvern Mastersizer 2000) by dispersing a 250 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. Sonication was maintained as the sample was stirred at 2500 rpm and measurements taken every 15 seconds, with the average of three measurements reported. 10 mg of TCA containing microparticles were added to 10 mL of dimethylsulfoxide (DMSO), mixed until dissolved and an aliquot analyzed by HPLC to determine the microparticle drug load. Another 4 mg of TCA containing microparticles were suspended in 20 mL of phosphate buffered saline (PBS) containing 0.5% sodium dodecyl sulfate (SDS) maintained at 37° C. 0.5 mL of the media was removed at regular intervals, replaced at each interval with an equivalent amount of fresh media to maintain a constant volume, and analyzed by HPLC to determine microparticle in vitro release. Analysis by HPLC was conducted using a C18 (Waters Nova-Pack C-18, 3.9×150 mm) and 35% acetonitrile mobile phase at 1 ml/min flow rate with UV detection at 240 nm. The results are shown in Table 10.

TABLE 10

Analytical Results of Triamcinolone Acetonide PLGA 50:50 Microparticle Formulations				
PLGA(lactide: glycolide molar ratio/ inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 20% TCA	19.2	96	D0.1: 30.0 μm D0.5: 48.5 μm D0.9: 77.0 μm	0.2 day: 2.1 1 day: 3.3 3 day: 17.0 7 day: 18.7 14 day: 21.0 21 day: 23.5 28 day: 25.6
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 25% TCA	23.9	95.6	D0.1: 30.2 μm D0.5: 48.2 μm D0.9: 75.8 μm	0.2 day: 4.0 1 day: 7.8 3 day: 21.1 7 day: 32.1 14 day: 39.2 21 day: 40.0 28 day: 40.8
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 30% TCA	29.3	97.6	D0.1: 31.5 μm D0.5: 48.0 μm D0.9: 68.9 μm	0.2 day: 5.1 1 day: 16.0 3 day: 33.6 7 day: 49.9 14 day: 54.0 21 day: 53.2 28 day: 52.2
50:50 carboxylic acid end-capped 0.18 dL/g 18 kDa 30% TCA	27.2	91	D0.1: 37.6 μm D0.5: 59.8 μm D0.9: 93.9 μm	0.2 day: 4.4 1 day: 9.8 3 day: 13.8 7 day: 17.7 14 day: 21.9 21 day: 26.3 28 day: 36.6
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 30% TCA 10% PEG 3350	30.4	101	D0.1: 38.1 μm D0.5: 56.6 μm D0.9: 82.1 μm	0.2 day: 4.2 1 day: 14.6 3 day: 32.2 7 day: 51.0 14 day: 60.1 21 day: 61.1 28 day: 60.1

TABLE 10-continued

Analytical Results of Triamcinolone Acetonide PLGA 50:50 Microparticle Formulations				
PLGA(lactide: glycolide molar ratio/ inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 35% TCA	34.4	98.3	D0.1: 35.1 μm D0.5: 52.3 μm D0.9: 75.6 μm	0.2 day: 7.1 1 day: 23.3 3 day: 47.6 7 day: 66.9 14 day: 69.3 21 day: 68.3 28 day: 66.7
50:50 ester endcapped 0.4 dL/g 66 kDa 25% TCA	23.2	93	D0.1: 34.2 μm D0.5: 51.7 μm D0.9: 77.4 μm	0.2 day: 3.1 1 day: 7.8 3 day: 12.5 7 day: 15.4 14 day: 16.2 21 day: 16.0 28 day: 16.4

In-vitro release profiles of the various PLGA (50:50) formulations are shown in the FIG. 19. The use of PLGA (50:50) did not improve the release kinetics of the triamcinolone acetonide as compared to the PLGA (75:25). Unexpectedly, 25% triamcinolone acetonide microparticles in PLGA (50:50) release the corticosteroid at a slower rate and give an incomplete release as compared to the equivalent amount of triamcinolone acetonide incorporated in PLGA 75:25. All the PLGA 50:50 formulation show a substantial lag phase, where little or any TCA is being released after 7 days, which continues to about day 50. As observed with TCA PLGA 75:25 formulations, increasing the amount of TCA increases the rate of release and allows for more TCA to be released before entering the lag phase. Similarly, the addition of PEG has minimal influence on the release rate of TCA, while lower molecular weight PLGA 50:50 decrease the release rate as observed with PLGA 75:25 formulations.

Based on the studies described herein, the Class B corticosteroid microparticle formulations, for example, the TCA microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 22%-28% of the microparticle; and (ii) the polymer is PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.3 to 0.5 dL/g, and or having a lactide:glycolide molar ratio of 80:20 to 60:40.

Example 5

Preparation of Triamcinolone Acetonide PLGA
Microparticles by Solid in Oil in Water (S/O/W)
Emulsion

A pharmaceutical depot was prepared comprised of the corticosteroid, triamcinolone acetonide (TCA, 9α-Fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-acetonide; 9α-Fluoro-16α-hydroxyprednisolone 16α,17α-acetonide) incorporated into microparticles.

Formulations were prepared by dissolving approximately 1 gram of PLGA in 6.67 mL of dichloromethane (DCM). To the polymer solution, 400 mg of triamcinolone acetonide was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to rotate at approximately 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the TCA incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 ml HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle samples, nominally 1 g were placed in 22 ml glass vials in 8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 µm; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 µm, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm.

In one group of suitable thirty day formulations, the PLGA is an ester end capped PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.71 dL/g and molecular weight of 114 kDa) with 10% or 20% triblock (TB) polymer (PLGA-PEG-PLGA). Triblock polymer was synthesized using a method described by Zentner et al 2001 (Zentner et al. "Biodegradable block copolymers for delivery of proteins and water-insoluble drugs." *J Control Release* 72 (2001): 203-15) and refined by Hou et al 2008 (Hou et al., "In situ gelling hydrogels incorporating microparticles as drug delivery carriers for regenerative medicine." *J Pharm Sci* 97(9) (2008): 3972-80). It is synthesized using a ring opening polymerization of cyclic dimers of D,L-lactide and glycolide with PEG 1,500 kDa in the presence of stannous octoate. In vitro release (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.40 dL/g and molecular weight of 66 kDa). The analytical results for these formulations are shown in Table 11.

TABLE 11

Analytical Results of Nominal 28.6% Triamcinolone Acetonide in PLGA 75:25 plus Triblock Microparticle Formulations					
PLGA(lactide:glycolide molar ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (%) TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, µm)	In vitro release (%)	
5 10 15 20 25 30	75:25 ester endcapped 0.71 dL/g 114 kDa 28.6% TCA 10% Triblock	23.8	83.2	D0.1: 38.9 µm	1 day: 8.2
				D0.5: 74.7 µm	2 day: 14.2
				D0.9: 103.0 µm	3 day: 15.7
					4 day: 18.2
					6 day: 28.8
					9 day: 38.9
					12 day: 49.8
					16 day: 61.6
					20 day: 66.4
					24 day: 68.7
35 40 45 50 55 60	75:25 ester endcapped 0.71 dL/g 114 kDa 28.6% TCA 20% Triblock (TB)	24.8	86.7		30 day: 72.3
					35 day: 72.8
				D0.1: 39.5 µm	1 day: 5.5
				D0.5: 74.6 µm	2 day: 8.9
				D0.9: 104.2 µm	3 day: 12.8
					4 day: 14.5
					6 day: 28.4
					9 day: 35.6
					12 day: 47.8
					16 day: 53.0
65 70 75 80 85 90					20 day: 64.3
					24 day: 67.3
					30 day: 73.0
					35 day: 73.0

The in vitro cumulative release profiles for both triblock containing formulations are shown in FIG. 20. The amount of triblock in the tested formulations did not influence the cumulative percent release.

In one iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. These calculated doses equal 149 mg of microparticles containing 35 mg of TCA and 252 microparticles containing 62 mg of TCA, for the 10% and 20% triblock formulations respectively (FIG. 21 and FIG. 22). In a second iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would not have an suppress the HPA axis, i.e. endogenous cortisol suppression more than 35%. These calculated doses equal 66 mg of microparticles containing 16 mg of TCA and 47 microparticles containing 12 mg of TCA, for the 10% and 20% triblock formulations respectively (FIG. 23 and FIG. 24).

In another suitable formulation lasting greater than 30 days and up to 90 days, the PLGA polymer consists of two different molecular weight PLGA 75:25 polymers in a two to one ratio, PLGA 75:25 (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.27 dL/g and molecular weight of 29 kDa) and ester end capped PLGA 5.5E (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.58 dL/g and molecular weight of 86 kDa), respectively. The formulation was processed as described above with the exception that 200 mg of triamcinolone acetonide was used in the formulation instead of 400 mg and similarly analyzed as describe for other formulations. The results are shown in the Table 12.

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TABLE 12

Analytical Results of a Nominal 16.7% Triamcinolone Acetonide in Mixed Molecular Weight PLGA 75:25 Microparticle Formulation				
PLGA (lactide: glycolide molar ratio) ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (%) TCA by weight	Incorporation efficiency (%)	Particle size (Dv, μm)	In vitro release (%)
75:25 ester endcapped	14.6	87.7	D0.1: 36.5 μm	1 day: 12.4
0.58 dL/g			D0.5: 54.0 μm	2 day: 21.6
86 kDa			D0.9: 69.4 μm	3 day: 27.3
And				4 day: 33.6
75:25 carboxylic acid end-capped				6 day: 41.2
0.27 dL/g				9 day: 50.7
29 kDa				12 day: 54.3
16.7% TCA				17 day: 62.0
				20 day: 73.1
				25 day: 75.5
				30 day: 82.9
				35 day: 84.6
				42 day: 87.4
				49 day: 89.2

In Vitro Cumulative Percent TCA Release Data is Graphed in FIG. 25.

In one iteration of these in vitro release data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. This calculated dose equals 317 mg of microparticles containing 46 mg of TCA. In a second iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would not have an suppress the HPA axis, i.e. endogenous cortisol suppression more than 35%. This calculated dose equals 93 mg of microparticles containing 14 mg of TCA.

Several other triamcinolone acetonide PLGA depots were formulated in the same manner as described above with different polymers including polycaprolactone (14 kDa), PLGA 50:50 (carboxylic acid end-capped, 0.44 dL/g, MW 56 kDa), PLGA 85:15 (carboxylic acid end-capped, 0.43 dL/g, 56 kDa) and a mixed molecular weight formulation using PLGA 75:25 (carboxylic acid end capped, 0.27 dL/g, MW 29 kDa) and PLGA 75:25 (ester end-capped, 0.57 dL/g, MW 86 kDa) in a two to one ratio. The in vitro cumulative percent release of triamcinolone acetonide is shown in FIG. 28. None of these formulations were suitable for a nominal thirty day or longer duration pharmaceutical depot. Polycaprolactone release all the triamcinolone acetonide prior to 14 days. The PLGA 50:50 microparticles released about 35% of its content by day 12 and then entered a lag phase where no drug was released up to 30 days. The PLGA 85:15 microparticles exhibited similar in vitro release kinetics as the PLGA 50:50, releasing about 30% of its content by day 12 and then entered a lag phase where no drug was released up to 30 days (See FIG. 28). A similar phenomenon is seen as shown in Example 4, where the mixed molecular weight PLGA 75:25 unexpectedly exhibits faster initial release of the triamcinolone acetonide than PLGA 50:50.

Based on the studies described herein, the Class B corticosteroid microparticle formulations, for example, the TCA microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 12%-28% of the microparticle; and (ii) the

polymer is (1) PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.3 to 0.5 dL/g, containing 10%-20% Triblock and/or having a lactide:glycolide molar ratio of 80:20 to 60:40 or (2) a mixture of low and high molecular weight PLGAs in a two to one ratio. The low molecular weight PLGA has a molecular weight of range of 15-35 kDa and an inherent viscosity range from 0.2 to 0.35 dL/g, and the high molecular weight PLGA has a range of 70-95 kDa and an inherent viscosity range of 0.5 to 0.70 dL/g.

Example 6

Preparation of Prednisolone PLGA Microparticles by Solid in Oil in Water (S/O/W) Emulsion

A pharmaceutical depot was prepared comprised of the corticosteroid, prednisolone (PRED, 11β,17,21-trihydroxy-pregna-1,4-diene-3,20-dione) incorporated into microparticles in PLGA 50:50.

Formulations were prepared by dissolving approximately 1 gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50, inherent viscosity 0.44 dL/g, MW 56 kDa) in 6.67 mL of dichloromethane (DCM). To the polymer solution, 400 mg of prednisolone was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to spin at 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the PRED incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 ml HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle samples, nominally 1 g were placed in 22 ml glass vials in 8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 μm; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 μm, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm. The analytical results are shown in the Table 13.

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TABLE 13

Analytical Results of a Nominal 28.6% Prednisolone in PLGA 50:50 Microparticle Formulation				
PLGA(lactide: glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% PRED by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, µm)	In vitro release (%)
50:50 carboxylic acid end-capped 0.44 dL/g 56 kDa 28.6% PRED	19.0	66.4	D0.1: 34.4 µm D0.5: 66.9 µm D0.9: 87.5 µm	1 day: 7.2 2 day: 11.5 3 day: 15.6 4 day: 20.2 5 day: 24.0 6 day: 28.4 7 day: 32.7 9 day: 36.5 11 day: 41.4 13 day: 45.0 15 day: 49.3 18 day: 52.0 21 day: 55.2 24 day: 58.3 27 day: 62.3 30 day: 65.9

In vitro release profile of the prednisolone PLGA micro-
particles is shown in FIG. 29. This formulation is suitable for
a 30 day formulation or greater.

In one iteration of the cumulative percent in vitro release
data, the amount of prednisolone released per day was calcu-
lated based on a human dose, as exemplified in Table 2, which
may achieve a temporary suppression of endogenous cortisol
(greater than 50%) and, within 14 days, achieve cortisol sup-
pression of endogenous cortisol of less than 35% (FIG. 30).
The calculated dose equals 699 mg of microparticles contain-
ing 133 mg of PRED. In a second iteration of these data, the
amount of PRED released per day was calculated based on a
human dose, as exemplified in Table 2 that would not suppress
the HPA axis, i.e. endogenous cortisol suppression of less
than 35% (FIG. 31). This calculated dose equals 377 mg of
microparticles containing 72 mg of PRED.

Based on the studies described herein, the Class A corti-
costeroid microparticle formulations, for example, the pred-
nisolone microparticle formulations, exhibiting the desired
release kinetics have the following characteristics: (i) the
corticosteroid is between 10%-40% of the microparticle, for
example, between 15%-30% of the microparticle; and (ii) the
polymer is PLGA having a molecular weight in the range of
about 45 to 75 kDa, having an inherent viscosity in the range
of 0.35 to 0.5 dL/g, and or having a lactide:glycolide molar
ratio of 60:40 to 45:55.

Example 7

Preparation of Betamethasone PLGA Microparticles
by Solid in Oil in Water (S/O/W) Emulsion

A pharmaceutical depot was prepared comprised of the
corticosteroid, betamethasone (BETA, 9-Fluoro-11β,17,21-
trihydroxy-16β-methylpregna-1,4-diene-3,20-dione) incor-
porated into microparticles in PLGA 50:50.

A formulation was prepared by dissolving approximately 1
gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50,
inherent viscosity 0.44 dL/g, MW 56 kDa) in 6.67 mL of
dichloromethane (DCM). To the polymer solution, 400 mg of
betamethasone was added and sonicated. Subsequently, the
corticosteroid containing dispersion was poured into 200 mL

of 0.3% polyvinyl alcohol (PVA) solution while homogeniz-
ing with a Silverson homogenizer using a rotor fixed with a
Silverson Square Hole High Shear Screen™, set to spin at
2,000 rpm to form the microparticles. After two minutes, the
beaker was removed, and a glass magnetic stirrer) added to
the beaker, which was then placed onto a multi-way magnetic
stirrer and stirred for four hours at 300 rpm to evaporate the
DCM. The microparticles were then washed with 2 liters of
distilled water, sieved through a 100 micron screen. The
microparticles were then lyophilized for greater than 96 hours
and vacuum packed.

Particle size of the BETA incorporated microparticles was
determined using laser diffraction (Beckman Coulter LS 230)
by dispersing a 50 mg aliquot in water, with the refractive
index (RI) for water and PLGA, set at 1.33 and 1.46 respec-
tively. The sample was stirred at the particle size measure-
ment measurements taken and the results reported. Drug load
was determined by suspending a nominal 10 mg of micropar-
ticles in 8 ml HPLC grade methanol and sonicating for 2
hours. Samples were then centrifuged at 14,000 g for 15 mins
before an aliquot of the supernatant was assayed via HPLC as
described below. Corticosteroid-loaded microparticle
samples, nominally 1 g were placed in 22 ml glass vials in
8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered
saline and stored in a 37° C. incubator with magnetic stirring
at 130 rpm. Each test sample was prepared and analyzed in
duplicate to monitor possible variability. At each time point in
the release study, microparticles were allowed to settle, and
an aliquot of between 4-16 ml of supernatant were taken, and
replaced with an equal volume of fresh 0.5% v/v Tween 20 in
100 mM phosphate buffered saline. Drug load and in vitro
release samples were analyzed by HPLC using a Hypersil
C18 column (100 mm, i.d. 5 mm, particle size 5 µm; Ther-
moFisher) and Beckman HPLC. All samples were run using
a sample injection volume of 5 µm, and column temperature
of 40° C. An isocratic mobile phase of 60% methanol and
40% water was used at a flow rate of 1 ml/min, with detection
at a wavelength of 254 nm. The analytical characteristics of
the betamethasone PLGA microparticles are shown in the
Table 14.

TABLE 14

Analytical Results of a Nominal 28.6% Betamethasone PLGA 50:50 Microparticle Formulation				
PLGA(lactide: glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% BETA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, µm)	In vitro release (%)
50:50 carboxylic acid endcapped 0.44 dL/g 56 kDa 28.6% BETA	22.8	79.7	D0.1: 42.1 µm D0.5: 71.7 µm D0.9: 102.7 µm	1 day: 2.0 2 day: 3.1 3 day: 4.8 4 day: 7.7 5 day: 12.5 6 day: 21.4 7 day: 30.8 9 day: 38.6 11 day: 43.9 13 day: 49.6 15 day: 55.5 18 day: 57.5 21 day: 59.2 24 day: 60.8 27 day: 62.9 30 day: 72.4

In vitro release profile of the betamethasone PLGA micro-particles is shown in FIG. 32. This formulation is suitable for a 30 day formulation or greater.

In one iteration of the in vitro release data, the amount of betamethasone released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. This calculated dose equals 111 mg of microparticles containing 25 mg of betamethasone. In a second iteration of these data, the amount of betamethasone released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35%. This calculated dose equals 38 mg of micro-particles containing 9 mg of betamethasone. These doses are both graphically represented in FIGS. 33 and 34.

Based on the studies described herein, the Class C corticosteroid microparticle formulations, for example, the betamethasone microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 10%-40% of the microparticle, for example, between 15%-30% of the microparticle; and (ii) the polymer is PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.35 to 0.5 dL/g, and or having a lactide:glycolide molar ratio of 60:40 to 45:55.

Example 8

Preparation of Fluticasone Propionate PLGA Microparticles by Solid in Oil in Water (S/O/W) Emulsion

A pharmaceutical depot was prepared comprised of the corticosteroid, fluticasone propionate (FLUT, S-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, 17-propionate) incorporated into microparticles in PLGA 50:50.

A formulation was prepared by dissolving approximately 1 gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50, inherent viscosity 0.45 dL/g, molecular weight 66 kDa) in 6.67 mL of dichloromethane (DCM). To the polymer solution, 200 mg of fluticasone propionate was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to spin at 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the FLUT incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 ml HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle

samples, nominally 1 g were placed in 22 ml glass vials in 8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 μ m; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 μ m, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm. The analytical results of the fluticasone propionate PLGA microparticles are shown in Table 15.

TABLE 15

Analytical Results of a Nominal 16.7% Fluticasone PLGA 50:50 Microparticle Formulation

PLGA(lactide:glycolide molar ratio)	Drug load (%)	Incorporation efficiency (%)	Particle size (Dv, μ m)	In vitro release (%)
ratio/inherent viscosity/molecular weight/target % FLUT/	FLUT by weight)			
50:50	8.5	51.1	D0.1: 34.1 μ m	1 day: 29.5
carboxylic acid endcapped			D0.5: 65.5 μ m	2 day: 43.5
0.45 dL/g			D0.9: 95.0 μ m	3 day: 46.7
66 kDa				4 day: 50.9
16.7% FLUT				5 day: 55.5
				6 day: 58.6
				7 day: 60.1
				9 day: 63
				11 day: 66.8
				13 day: 67.8
				15 day: 68.7
				18 day: 73.7
				21 day: 81.8
				24 day: 93.7
				26 day: 97.1
				31 day: 100.8

In vitro release profile of the fluticasone propionate PLGA microparticles is shown in FIG. 35. This formulation is suitable for a 30 day formulation or greater.

In one iteration of the in vitro release data, the amount of fluticasone propionate released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. This calculated dose equals 178 mg of microparticles containing 15 mg of fluticasone propionate. In a second iteration of these data, the amount of fluticasone propionate released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35%. This calculated dose equals 24 mg of microparticles containing 2 mg of fluticasone propionate. These doses are both graphically represented in FIGS. 36 and 37.

Other fluticasone propionate PLGA depots were formulated in the same manner as described above with different PLGA polymers or amounts fluticasone propionate. In one formulation, a PLGA polymer with a higher lactide to gly-

colide ratio (PLGA 75:25 (ester end-capped PLGA 75:25, lactide:glycolide molar ratio of 75:25, 0.58 dL/g, MW 86 kDa) was used instead of the PLGA 50:50 as previously described. Unlike the triamcinolone acetonide preparations described in Example 5, but typically expected as described in the literature, the higher lactide to glycolide ratio resulted in a slower release, where 30% release in 14 days, followed by a substantial lag phase where little drug is released for a minimum of thirty days. In another example, 400 mg of fluticasone propionate instead of 200 mg was used in preparation of PLGA 50:50 microparticles (target drug load 28.6%). Unlike triamcinolone acetonide microparticle preparations, the higher drug load did not result in a significantly different release of fluticasone propionate; FIG. 38 shows the in vitro release of all three fluticasone propionate formulations.

Based on the studies described herein, the Class D corticosteroid microparticle formulations, for example, the fluticasone or fluticasone propionate microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 8%-20% of the microparticle, and (ii) the polymer is PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.35 to 0.5 dL/g, and or having a lactide:glycolide molar ratio of 60:40 to 45:55.

Example 9

Preparation of Dexamethasone Microparticles by Solvent Dispersion in PLGA

A pharmaceutical depot was prepared comprised of the corticosteroid, dexamethasone (DEX, 9-Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione) incorporated into microparticles in PLGA 50:50.

A formulation was prepared by dissolving approximately 1 gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50, inherent viscosity 0.45 dL/g, molecular weight 66 kDa) in 6.67 mL of dichloromethane (DCM). To the polymer solution, 200 mg of dexamethasone was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to spin at 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer) added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the DEX incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 ml HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle samples, nominally 1 g were placed in 22 ml glass vials in

8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 μ m; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 μ m, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm. The analytical results for the dexamethasone PLGA microparticles are shown in Table 16.

TABLE 16

Analytical Results of a Nominal 28.6% Dexamethasone PLGA 50:50 Microparticle Formulation					
PLGA(lactide:glycolide molar ratio/inherent viscosity/molecular weight/target weight/ % FLUT/	Drug load (%) DEX by weight)	Incorporation efficiency (%)	Particle size (Dv, μ m)	In vitro release (%)	
50:50	22.1	77.2	D0.1: 41.2 μ m	1 day: 2.9	
carboxylic acid endcapped			D0.5: 71.9 μ m	2 day: 4.6	
0.45 dL/g			D0.9: 99.1 μ m	3 day: 6.3	
66 kDa				4 day: 8.7	
28.6% DEX				5 day: 10.9	
				6 day: 12.7	
				7 day: 15.0	
				9 day: 16.4	
				11 day: 18.0	
				13 day: 20.7	
				15 day: 24.6	
				18 day: 26.2	
				21 day: 28.1	
				24 day: 30.3	
				27 day: 34.0	
				30 day: 46.3	

In vitro cumulative percent release of the dexamethasone is shown in 39, and results in suitable formulation for a minimum of thirty days and, assuming linear release, likely up to 60 days.

In one iteration of the in vitro release data, the amount of dexamethasone released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. In a second iteration of these data, the amount of dexamethasone released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35%. In the case of dexamethasone, where the data is truncated, both calculated human doses are the same; 36 mg of microparticles containing 8 mg of dexamethasone. The doses are graphically represented in FIG. 40.

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Example 10

Pharmacology, Pharmacokinetics and Exploratory
Safety Study of Corticosteroid Formulations

In an exploratory safety study in rats, single intra-articular (IA) doses of TCA immediate release (TCA IR) (0.18 and 1.125 mg) and doses of TCA in 75:25 PLGA formulation microparticles (FX006) (0.28, 0.56 and 1.125 mg (i.e., the maximum feasible dose) of TCA) were evaluated. Blood samples were collected at various time points for determination of plasma concentrations. Plasma concentration-time data from this study and pharmacokinetic (PK) analysis thereof are shown in FIGS. 41-43 and Tables 17-20.

As seen in FIGS. 41A-41D, FX006 dosed at 1.125 mg resulted in a very slow absorption of TCA in the systemic circulation and a markedly lower C_{max} as compared to TCA IR.

As shown in Table 17, the mean AUC_{0-24} values of TCA following 1.125 mg administration of FX006 were 2.1-fold lower than those observed for TCA IR (i.e., 2856 vs. 6065 ng·h/mL, respectively). The mean C_{max} values of TCA following 1.125 mg administration of FX006 were 15-fold lower than those observed for TCA IR (i.e., 125 vs. 8.15 ng/mL, respectively). The absorption of TCA following administration of FX006 was slower than that observed for TCA IR, with mean T_{max} values observed at 3.33 and 1.00 h, respectively. The elimination half-life of TCA following administration of 1.125 mg FX006 and TCA IR were 451 and 107 h, respectively.

TABLE 17

Summary of TCA Plasma Pharmacokinetic Parameters										
Variable	Treatment									
	FX006 (0.28 mg)		FX006 (0.56 mg)		FX006 (1.125 mg)		TCA IR (0.18 mg)		TCA IR (1.125 mg)	
	Mean	(CV %)	Mean	(CV %)	Mean	(CV %)	Mean	(CV %)	Mean	(CV %)
AUC ₀₋₂₄ (ng · h/mL)	31.0	(76.0)	33.0	(19.1)	136	(6.0)	297	(21.5)	1403	(13.2)
AUC _{0-∞} (ng · h/mL)	356	(62.0)	572	(21.5)	2856	(17.2)	479	(32.6)	6065	(3.7)
AUC ₀₋₇ (ng · h/mL)	335	(66.5)	532	(23.8)	2142	(14.4)	456	(31.3)	6013	(3.4)
Cl/F (mL/h)	1308	(96.6)	1014	(24.4)	403	(19.1)	400	(27.6)	186	(3.6)
C _{max} (ng/mL)	1.82	(66.2)	1.91	(10.2)	8.15	(12.5)	41.6	(25.1)	125	(5.3)
T _{1/2} (h)	99.5	(39.9)	180	(27.0)	451	(20.8)	35.6	(63.5)	107	(56.7)
T _{max} (h)	17.7	(148.9)	16.7	(162.8)	3.33	(69.3)	2.00	(0.0)	1.00	(0.0)
V _{ss} /F (mL)	274215	(117.0)	326966	(30.2)	240481	(17.7)	12069	(53.4)	23829	(34.4)

The above results suggest a slower distribution and bioavailability of TCA in the systemic circulation following administration of FX006 as compared to TCA IR. Without wishing to be bound by theory, the slower distribution FX006 into the systemic circulation may be related to the longer residence time of FX006 at the site of injection. This is supported by the lesser availability of the FX006 microparticle formulation in the early “burst” phase, where only 4-9% of product is released, compared to at least 23% of the IR product.

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Bioavailability of TCA in the systemic circulation following administration of FX006 was 3-fold lower than that observed for TCA IR, as shown in Table 18.

TABLE 18

Bioavailability of TCA in Plasma		
Absolute Bioavailability Comparison		
	FX006 (0.28 mg)	TCA IR (0.18 mg)
F_{abs} (%)	17.9	58.6

For the 0.56 and 1.125 mg dose levels of FX006, apparent F % were 23.1% and 58.1%, respectively. The IV data in rats shown in Table 19 was used as a reference to calculate F.

TABLE 19

Pharmacokinetic Parameters of TCA in Rat Plasma After i.v. (50 mg/kg bolus + 23 mg/kg/h Infusion) Administration of Triamcinolone Acetonide Phosphate				
Parameter	Rat 1	Rat 2	Rat 3	Mean ± SD
V_c (L/kg)	0.684	0.856	1.29	0.944 ± 0.314
CL (L/h/kg)	1.15	0.790	0.872	0.937 ± 0.188
k_{12} (h ⁻¹)	1.64	1.79	1.59	1.67 ± 0.102
k_{21} (h ⁻¹)	1.04	0.640	1.13	0.937 ± 0.261

TABLE 19-continued

Pharmacokinetic Parameters of TCA in Rat Plasma After i.v. (50 mg/kg bolus + 23 mg/kg/h Infusion) Administration of Triamcinolone Acetonide Phosphate				
Parameter	Rat 1	Rat 2	Rat 3	Mean ± SD
$T_{1/2}$ (h)	1.55	3.71	2.87	2.71 ± 1.09
f_u	0.084	0.110	0.085	0.093 ± 0.015

from Rojas et al., “Microdialysis of triamcinolone acetonide in rat muscle,” *J Pharm Sci* 92(2) (2003): 394-397.

The initial “burst” (i.e., exposure up to 24 h) accounted for less than 10% of the total systemic exposure of FX006. The initial burst accounted for ~23-62% of the total exposure for the TCA IR product, as shown in Table 20.

TABLE 20

Variable	Relative Availability of TCA in Plasma (Initial Burst vs. Delayed Release)				
	Treatment				
	FX006 (0.28 mg) Mean	FX006 (0.56 mg) Mean	FX006 (1.125 mg) Mean	TCA IR (0.18 mg) Mean	TCA IR (1.125 mg) Mean
AUC ₀₋₂₄ (ng · h/mL)	31.0	33.0	136	297	1403
AUC _{0-∞} (ng · h/mL)	356	572	2856	479	6065
AUC _{24-∞} (ng · h/mL)	325	539	2720	182	4662
% Initial Burst	8.69	5.76	4.76	62.1	23.1

In this same study, groups of animals were sacrificed 28 days after dosing, and the remaining were terminated on Day 42. Body weights were monitored throughout the study and key organs (spleen, adrenal glands, thymus) were weighed upon necropsy. The injected knee and the contralateral control joints were prepared for histological assessment. Toluidine blue stained sections of joints were evaluated for treatment-related alterations. Histologic changes were described, wherever possible, according to their distribution, severity, and morphologic character.

Histological analysis demonstrated the following observations. First, injected joints from placebo (blank PLGA microspheres)-treated animals had minimal multifocal macrophage infiltration in associated with 20-130 μm diameter microspheres, whereas none of the active FX006-injected joints showed the presence of any microspheres at Day 28. Placebo-treated rat joints had no cartilage or joint changes save for the presence of spontaneous cartilage cysts in a few joints (1 at Day 28, 2 at Day 42) in the right (injected) knees. The left knees in the placebo-treated rat joints were normal. In comparison, both knees in the high dose TCA IR and the high and mid-dose FX006-groups showed some mild bone marrow hypocellularity and growth plate atrophy (dose dependent for FX006). Both knees in the low dose TCA IR and FX006 animals were normal. Spontaneous cartilage cysts noted in placebo animals were also noted in all groups dosed with FX006 with no increase in incidence or severity. High dose TCA IR increased cartilage cysts at Day 42 but not at Day 28. In general, FX006-treated animals had normal articular cartilage despite the presence of catabolic effects on other joint structures, which was likely more readily observed on account of the young age of the animals.

Overall, all observed effects of FX006, especially at the high dose, such as body weight loss and reduced organ weights were also seen with TCA IR. The time course of inhibition of the HPA axis (measured as corticosterone levels) is shown in FIG. 42. It should be noted that at the lowest dose of FX006 (0.28 mg; circles) corticosterone levels were initially inhibited but recovered back to near baseline by Day 14 post-dose. Similarly, with TCA IR at the lowest dose (0.18 mg), corticosterone levels recovered by Day 7 (squares). With the mid (0.56 mg) and high (1.125 mg) doses of FX006 and the high dose of TCA IR (1.125 mg), corticosterone levels were inhibited longer as shown in FIG. 42.

A PK-PD analysis demonstrated that inhibition of corticosterone was correlated with systemic TCA levels and followed a classical inhibitory model as shown in FIG. 43. The IC₅₀ was about 1 ng/mL and the E_{max} was achieved at 50-80 ng/mL.

Example 11

Evaluation of Efficacy of Single Doses of TCA Immediate Release and TCA Microparticle Formulation in Animal Model of Osteoarthritis

The studies described herein were designed to test and evaluate the efficacy of the corticosteroid microparticle formulations provided herein as compared to immediate release corticosteroid formulations. While the studies herein use TCA, it is understood that other corticosteroids, including other Class B corticosteroids, Class A corticosteroids, Class C corticosteroids, and Class D corticosteroids, can be evaluated using these materials, methods and animal models.

Efficacy of single intra-articular (IA) doses of FX006 (TCA in 75:25 PLGA formulation microparticles) and TCA IR (immediate release) was evaluated in a rat model of osteoarthritis of the knee via sensitization and challenge by peptidoglycan polysaccharide (PGPS). The model involves priming the animals with an intra-articular injection of PGPS in the right knee. The following day, any animals with no knee discomfort were eliminated from the test article groups and placed into the baseline group. Two weeks later, knee inflammation was reactivated by a tail vein injection of PGPS, 2.5 hr following IA dosing with FX006 or TCA IR at the doses selected (n=10/group). Differences in weight-bearing and gait (as a measure of joint pain experienced by the animals), histopathology, plasma PK etc. were evaluated.

Doses of FX006 (0.28, 0.12, 0.03 mg) and TCA IR (0.06, 0.03 mg) for this study were selected based on data from the study described above in Example 10 and an initial run of the PGPS model in which only TCA IR was evaluated at two IA dose levels. The goals of the present study were to demonstrate the following:

FX006 is efficacious at doses that do not inhibit the HPA axis

The duration of efficacy is a function of dose

FX006 provides more prolonged pain relief as compared to TCA IR—Since only about 10% of the TCA payload is expected to be released from FX006 in the first 24 hr, one TCA IR dose group (0.03 mg) was chosen to match 10% of the TCA in FX006 at a dose of 0.28 mg

Effects of matched doses of FX006 and TCA IR (0.03 mg)

The duration of efficacy was assessed by 3 different reactivations, 2 weeks apart. After that point, the arthritis observed in the animals becomes more wide-spread making the efficacy in the index knee more difficult to assess.

At the first reactivation, vehicle treated animals demonstrate painful gait as demonstrated by high pain scores (3.5 out of a maximum of 4 possible) as shown in FIGS. 44A, 44B, and 44C. FX006 at 0.28 mg (squares) showed good efficacy. In the previous study described in Example 10, this dose was demonstrated to inhibit the HPA axis immediately after dosing but a return to baseline function was demonstrated by Day 14. Interestingly, this dose of FX006 continued to be efficacious upon the 2nd and 3rd reactivations on Days 14 and 28 when the HPA axis function was presumably normal. It should also be noted that since HPA axis function returned to baseline by Day 7 at a 0.18 mg dose of TCA IR in the previous study described in Example 10, the effects of the doses of TCA IR used in the present study (0.06 and 0.03 mg) were

also in the presence of normal HPA axis function following an initial transient inhibition. Corticosterone measurements from the present study (as an indicator of HPA axis function) are presented as change from baseline for each treatment group in FIG. 46. As demonstrated from these data, corticosterone levels for all groups recovered by Day 14; hence the goal of prolonged efficacy with FX006 in the presence of normal HPA axis function was achieved.

Overall, a clear dose-dependence of response was noted for both FX006 and TCA IR. Also, if less than 10% of this dose is available by the day after dosing (Day 1), it should be noted in FIG. 44B that the efficacy of FX006 at 0.28 mg (squares) is greater than TCA IR at 0.03 mg (triangles) at all evaluations. Further, the duration of efficacy of TCA (both FX006 and IR) appears to be a function of dose, however, the prolonged release of TCA from the PLGA microspheres in FX006 results in more sustained efficacy. This is more clearly depicted in another representation of the data in FIG. 45 in which peak response for each dose as determined by gait/pain scores on Day 1 following each reactivation (Days 1, 15 and 29) are plotted. FIG. 46 plots the time course of corticosterone recovery for all study groups. On balance, across all groups that received the corticosteroid, there was recovery.

Plasma levels of TCA were measured in samples taken from all rats at baseline (Day -4), Days 0 (2 hr post dosing), 1, 3, 8, 14, 17, 21, 28, and 31. Concentration-time curves for all treatment groups are shown in FIG. 47A. FIG. 47B shows only the FX006 dose groups on a larger scale since maximal plasma concentrations with FX006 were far lower than those with TCA IR.

Histopathological evaluation of the knees taken from all animals at the end of the study (Day 32 at the end of the 3rd reactivation of arthritis) demonstrated statistically significant improvement by FX006 at the high and mid-range doses (0.28 and 0.12 mg) in the composite histological score and each component score (inflammation, pannus, cartilage damage and bone resorption) as shown in FIG. 48. As described above, the dose of 0.28 mg FX006 demonstrated strong efficacy (i.e. analgesic activity) throughout all 3 reactivations, whereas the dose of 0.12 mg was active but to a lesser degree through all 3 reactivations. At the doses of TCA IR used, the duration of efficacy was mostly through the first reactivation of arthritis, with partial efficacy of the higher (0.06 mg) dose in the second reactivation, and this also translated into a much smaller non-significant improvement in histological scores. Importantly, these data demonstrate that TCA has no deleterious effect on cartilage and as has been described in other settings, it actually reduces cartilage damage in an inflammatory milieu.

In conclusion, the prolonged residence of TCA in the joint upon IA dosing with FX006 resulted in extending the duration of efficacy in the rat PGPS model of arthritis with a significant histological improvement in inflammation, pannus formation, cartilage damage and bone resorption. FX006 had these effects without inhibiting HPA axis function as demonstrated by the return to baseline of corticosterone levels within 14 days after dosing. The clinical implications for the treatment of patients with osteoarthritis, rheumatoid arthritis and other inflammatory joint disorders are as follows:

Intra-articular injection of sustained release corticosteroid microparticle formulations provides prolonged pain relief relative to intra-articular injection of immediate release steroids.

Intra-articular injection of sustained release corticosteroid microparticle formulations is efficacious in reducing pain and inflammation at doses that do not inhibit the HPA axis.

The duration of efficacy of sustained release of intra-articular corticosteroid microparticle formulations is a function of dose.

Intra-articular injection of sustained release corticosteroid microparticle formulations slows, arrests, reverses, or otherwise inhibits structural damage to tissues caused by inflammation.

Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims, which follow. In particular, it is contemplated by the inventors that various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. Other aspects, advantages, and modifications are considered to be within the scope of the following claims. The claims presented are representative of the inventions disclosed herein. Other, unclaimed inventions are also contemplated. Applicants reserve the right to pursue such inventions in later claims.

What is claimed is:

1. An injectable formulation comprising (a) controlled- or sustained-release microparticles comprising triamcinolone acetonide (TCA) or a pharmaceutically-acceptable salt thereof and a poly(lactic-co-glycolic) acid copolymer (PLGA) matrix, wherein the TCA comprises between 22% to 28% of the microparticles and wherein the PLGA has the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; and (ii) a lactic acid:glycolic acid molar ratio of 80:20 to 60:40, and wherein the TCA is released for between at least 14 days and 90 days upon administration to a joint.
2. The formulation of claim 1, wherein the PLGA copolymer has a molar ratio of lactic acid:glycolic acid of 75:25.
3. The formulation of claim 1, wherein the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle.
4. The formulation of claim 1, wherein the 22% to 28% of TCA in the microparticles comprises a total TCA load dose between 10 to 50 mg.
5. The formulation of claim 1, wherein the lactic acid:glycolic acid copolymer has an inherent viscosity in the range of 0.3 to 0.5 dL/g.
6. An injectable formulation comprising (a) controlled- or sustained-release microparticles comprising triamcinolone acetonide (TCA) or a pharmaceutically-acceptable salt thereof and a poly(lactic-co-glycolic) acid copolymer (PLGA) matrix, wherein the TCA comprises between 22% to 28% of the microparticles, wherein the microparticles have a mean diameter of between 10 μ m to 100 μ m, and wherein the PLGA has the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; and (ii) a lactic acid:glycolic acid molar ratio of 80:20 to 60:40, wherein the TCA is released for between at least 14 days and 90 days upon administration to a joint.
7. The formulation of claim 6, wherein the PLGA copolymer has a molar ratio of lactic acid:glycolic acid of 75:25.
8. The formulation of claim 6, wherein the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle.
9. The formulation of claim 6, wherein the 22 to 28% of TCA in the microparticles comprises a total TCA load dose between 10 to 50 mg.

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10. The formulation of claim 6, wherein the lactic acid-glycolic acid copolymer has an inherent viscosity in the range of 0.3 to 0.5 dL/g.

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