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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

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D.

REF: EXPEDIENTE 11-165-084

TÍTULO SOLICITADO: "SOLUCIÓN BEBIBLE FARMACÉUTICA DE TELMISARTAN"

PUBLICACIÓN: Gaceta 647 de 29 de Junio de 2012, N° de publicación 844.

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SOLICITANTE: BOHERINGER INGELHEIM VETMEDICA, GMBH

APODERADO: CARLOS R. OLARTE

TRÁMITE: SUSTENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42, inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 27 de Septiembre de 2012, en los siguientes términos:

I. RATIFICACIÓN

Comendidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los

artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

La mencionada solicitud colombiana se refiere a una solución farmacéutica para beber con un pH de 10 o superior que contiene un antagonista de la angiotensina II, preferiblemente Telmisartán, y excipientes para mejorar el sabor y prolongar la vida útil de la composición como alcoholes de azúcares, el objeto de la solicitud no puede adjudicársele novedad o nivel inventivo, ya que como mencioné en mi memorial de oposición, el descubrimiento de las condiciones apropiadas de una concentración de azúcar-alcoholes en una formulación de un antagonista de angiotensinas no obedece a una invención propiamente dicha sino a una estandarización y desarrollo de una formulación ya divulgada empleada en un ejemplo particular.

Como ya se ha mencionado en el memorial de oposición, la reivindicación principal se refiere a una composición que contiene : “un antagonista del receptor de angiotensina II” y “uno o mas azucres-alcoholes hasta una concentración de 40% a 70% (de preferencia 60%-70%)”.

De esta forma se observó que la solicitud no define su composición por sus componentes sino que se limita a mencionar grupos farmacológicos completos como “*antagonista del receptor de angiotensina II*”, y “uno o más azucres-alcoholes” los cuales abarcan un gran número de elementos activos. Se demostró que de dichos compuestos, únicamente se encuentra soportado el Telmisartán (ejemplos 1 a 8), y por consiguiente, la materia reclamada es una extrapolación irrazonable de ingredientes activos.

Así mismo, los alcoholes empleados son exclusivamente manitol, xilitol y sorbitol, por lo que la materia reclamada por la solicitud no presenta soporte ni comprobación de su efecto técnico por lo que no puede ser objeto de patente. Adicionalmente que el Solicitante no está definiendo claramente la composición en la reivindicación 1 en términos de los porcentajes de cada uno de los componentes, ni los componentes definidos técnicamente como parte de la composición allí sugerida.

Se observó además que se han reclamado alcoholes como isomalt y eritrita, los cuales no poseen soporte en la descripción y no son términos técnicos que definan el compuesto específico. Adicionalmente se comentó que la reivindicación 18 define otro tipo de invención dado que no se refiere a una característica técnica estructural que haga parte de la composición sino a un recipiente, lo cual no se considera al campo de la Química Farmacéutica.

Ahora, sobre los criterios de novedad se analizó el documento **US2007/026026** (2007-02-01), el cual divulga composiciones líquidas de Losartán con excipientes para lograr un pH mayor de 9 (página 13, reivindicación 1), mas específicamente presenta un pH entre 7 y 10 (página 13, reivindicación 2).

Dicho documento en la figura 5 muestra la estabilidad de la composición de Losartán en soluciones de glicol, glicerina y xilitol o cual demuestra que los “alcoholes-azucares” ya habían sido empleados en otras composiciones anteriores a las acá reclamadas, dando buenos resultados y pH entre 7 y 10. Así mismo, la anterioridad ya contemplaba la inclusión en su composición de alcoholes azucarados como el manitol como se observa en el párrafo 0055.

En síntesis la comparación de las características esenciales puede observarse en la siguiente tabla:

Características esenciales de la solicitud	US2007/026026
Solución farmacéutica con un valor de pH 10 o superior que contiene un antagonista del receptor de angiotensina II, caracterizada porque	Párrafo 42, página 3 Reivindicación 1, página 13;
Están contenidos uno o más azucares-alcoholes hasta una concentración total de 40% a 70%,	Párrafo 55, página 5

Se analizó por otro lado la ausencia de nivel inventivo en modalidades particulares de la solicitud empleando la anterioridad mencionada y en casos particulares el documento **WO2004/028505**, el cual revelaba ya composiciones de antagonistas de receptores de la angiotensina II, específicamente de Telmisartán (página 2), concluyendo que el técnico medio al estar tratando de resolver el problema de proveer composiciones líquidas de antagonistas del receptor de la angiotensina ii habría encontrado en D1 y D2 las enseñanzas que le permitirían llegar a formular composiciones como las reclamadas por la presente solicitud, en la cuales se

busca estabilidad y formulaciones adecuadas para el Telmisartán dada su sensibilidad frente al pH.

II. COMPLEMENTO DE INFORMACION

Adicional a lo expresado anteriormente, es necesario indicar que la solicitud en estudio no presenta los requisitos mínimos para ser objeto de patente ya que las reclamaciones formuladas en su capítulo reivindicatorio no definen una invención mediante sus características técnicas estructurales.

Aparte de los ejemplos ya mencionados, se observa que las características descritas en el capítulo reivindicatorio no obedecen a componentes técnicos sino a una descripción de las propiedades necesarias a alcanzar por la solicitud, esto obedece por ejemplo a que la solución sea "bebible", que el contenido sea máximo de 1000ppm (entre otros) de azúcares, un "agente conferidor de consistencia" "una base farmacéuticamente aceptable", un "antagonista de receptor de angiotensina", etc.

Se puede observar que todas estas propiedades no corresponden con una definición técnica de los componentes sino más bien una descripción de lo que se requiere lograr, dando como resultado una falta de claridad en la delimitación de los componentes.

Adicional a lo anterior, se observó que los documentos del estado de la técnica poseen todas las características técnicas reclamadas en las reivindicaciones de la solicitud en trámite, e incluso cuando se habla del compuesto antagonista de receptor de agiotensina II el cual se selecciona de Telmisartan, por lo que la objeción por novedad se extiende por completo a todo el capítulo reivindicatorio de la presente solicitud.

A pesar que el documento **US2007/026026** no menciona específicamente el Telmisartán como el componente seleccionado, esto no puede conferir novedad en la medida en que el Losartán divulgado por la anterioridad es un conocido inhibidor de angiotensina II al igual que Telmisartán indicando para cualquier técnico medio en la materia la opción de seleccionar un compuesto de cualquiera de los dos mencionados; esto implica que únicamente se trata de una solicitud de

patente de selección en la que compuestos intercambiables se reclaman para hacer uso de un privilegio de no mención expresa, pero que se encuentra divulgado en el estado de la técnica.

Por otro lado, al reivindicarse todos los compuestos inhibidores de angiotensina II en la solicitud en su reivindicación principal, se está haciendo mención expresa de que la selección específica de cualquiera de dichos compuestos no conferiría nivel inventivo a la solicitud ya que todos sirven para el mismo fin al solucionar el problema propuesto por el solicitante.

De esta manera aclaramos que la selección del Telmisartán dentro de la solicitud no podría ser tomada en cuenta como criterio de altura inventiva ya que obedece a una selección de uso normal en la técnica para cualquier persona que reconozca la necesidad de incluir en la formulación algún inhibidor de angiotensina II.

Ahora, con relación al documento **WO2004/028505** se observa que hace alusión a la composición farmacéutica de Telmisartán en una concentración de 3-50% en peso dispersa en una matriz que contiene: a) un agente básico en una proporción de Telmisartán entre 1:1 y 10:1, b) una sustancia tensoactiva entre 1- 20% en peso de la composición final, c) agua en una proporción de 25-70% en peso y opcionalmente d) en una proporción de 0-20% de sustancias auxiliares adicionales como azúcar-alcoholes tales como eritritol, sorbitol, manitol, dulcitol, ribitol, xilitol.

Se deja de presente que la selección de parámetros óptimos en una formulación obedece a técnicas rutinarias que pueden ser llevadas a cabo por cualquier persona medianamente versada en la materia y que son de obligatoria estandarización en cualquier composición farmacéutica. Por lo tanto, la determinación de parámetros óptimos de pH, entre otros, no puede ser causal de nivel inventivo o novedad en una composición ya que no ejerce un efecto sorprendente o ventajoso sobre el evidente del cambio de dichas condiciones.

De cualquier forma, las ventajas de las concentraciones, y parámetros definidos por la solicitud en comparación con el estado de la técnica mencionado, no son indicadas y por lo tanto no se asocia un efecto sorprendente o inesperado que pueda ser probado.

Por todo lo anterior, no existe diferencia evidente entre la solicitud en trámite y el estado de la técnica, en consecuencia, no puede ser objeto de patente lo revelado en el expediente 11-161-167.

III. ANEXOS

- Publicación internacional US 2007/0026026, Feb. 1, 2007, ORAL LIQUID LOSARTAN COMPOSITIONS, página 3, 5, 13
- Publicación internacional WO2004/028505, Sep 12, 2007, SOLID PHARMACEUTICAL FORMULATIONS COMPRISING TELMISARTAN, páginas 1 a 5

Señor Superintendente,



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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SOLID PHARMACEUTICAL FORMULATIONS COMPRISING TELMISARTAN

(57) Abstract: The invention relates to new solid pharmaceutical compositions comprising the angiotensin II receptor antagonist telmisartan, a basic agent, a surfactant or emulsifier and a water-soluble diluent, e.g. in form of granules or in form of a powder, as well as solid oral formulations ready for use/ingestion, e.g. capsule and tablet formulations made from said pharmaceutical compositions, and methods for producing said compositions and formulations making use of a fluid-bed granulation process or of a spray-drying process.

WO 2004/028505 A1

SOLID PHARMACEUTICAL FORMULATIONS COMPRISING TELMISARTAN

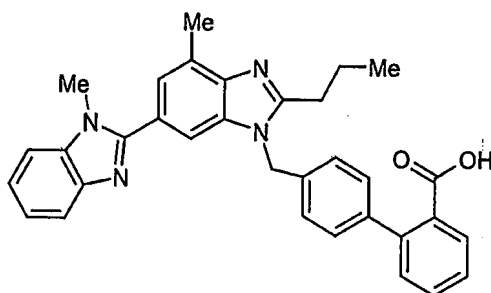
FIELD OF THE INVENTION

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The present invention relates to new solid pharmaceutical compositions comprising the angiotensin II receptor antagonist telmisartan, e.g. in form of granules or in form of a powder, as well as solid oral formulations ready for use/ingestion, e.g. capsule and tablet formulations made from said pharmaceutical compositions. The present
10 invention also provides methods for producing said compositions and formulations.

BACKGROUND OF THE INVENTION

INN Telmisartan is an angiotensin II receptor antagonist developed for the treatment
15 of hypertension and other medical indications as disclosed in EP-A-502314. Its chemical name is 4'-[2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-ylmethyl]-biphenyl-2-carboxylic acid having the following structure:



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Telmisartan is generally manufactured and supplied in the free acid form. As disclosed in WO 00/43370, crystalline telmisartan exists in two polymorphic forms having different melting points. Under the influence of heat and humidity, the lower melting polymorph B transforms irreversibly into the higher melting polymorph A.
25 Both forms are characterized by a very poor solubility in aqueous systems at the physiological pH range of the gastro-intestinal tract of between pH 1 to 7.

Telmisartan is obtainable on the market under the trade name Micardis®. Starting from the free acid form Telmisartan as introduced to the market is manufactured using an expensive spray-drying process. Due to the poor solubility of the free acid form preparation of alternative telmisartan formulation is difficult.

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BRIEF SUMMARY OF THE INVENTION

There is a clear need to provide alternative solid oral formulations of Telmisartan which can be prepared using less complicated and expensive processes and fulfill all prerequisites for pharmaceutical use, i.e. long-lasting stability of the formulation under different climatic conditions and sufficient solubility of the active substance for sufficient gastrointestinal absorption in the slightly acidic and neutral pH region.

It is a first object of the invention to provide said alternative solid pharmaceutical compositions comprising telmisartan, e.g. in form of granules or a powder, in a form allowing that the active compound is released with sufficient solubility for gastrointestinal absorption in the slightly acidic and neutral pH region from said compositions and formulations.

Preferably, the formulations should have immediate release characteristics and a dissolution showing no essential pH dependency within the physiological relevant pH interval of the gastrointestinal tract.

It is a second object of the invention to provide further solid oral formulations ready for use/ingestion, e.g. capsule and tablet formulations, made from said pharmaceutical compositions mentioned under the first aspect of the invention.

A third object of the invention relates to methods for producing said compositions and formulations mentioned hereinbefore.

DETAILED DESCRIPTION OF THE INVENTION

First object of the invention (pharmaceutical composition)

Surprisingly it has been found that the solubility of telmisartan can be raised by a factor of several hundreds by a pharmaceutical composition comprising 3 to 50 wt.% of telmisartan dispersed in a dissolving matrix comprising

- (a) a basic agent in a molar ratio of basic agent : telmisartan = 1:1 to 10:1,
 - (b) a surfactant or emulsifier in an amount of about 1 to 20 wt.% of the final composition ,
 - (c) 25 to 70 wt.% of a water-soluble diluent, and
 - (d) optionally 0 to 20 wt.% of further excipients and/or adjuvants,
- the sum of all components adding to 100%.

The term "dissolving tablet matrix" refers to a pharmaceutical tablet base formulation having immediate release (fast dissolution) characteristics that readily dissolves in a physiological aqueous medium.

Specific examples of suitable basic agents are alkali metal hydroxides such as NaOH and KOH; furthermore NaHCO₃, KHCO₃, Na₂CO₃, K₂CO₃, Na₂HPO₄, K₂HPO₄; basic amino acids such as arginine; and meglumine (N-methyl-D-glucamine).

The surfactants and emulsifiers may be ionic or non-ionic, the latter being preferred. Specific examples of surfactants and emulsifiers are such as poloxamers or pluronics, polyethylene glycols, polyethylene glycol monostearate, polysorbates, sodium lauryl sulfate, polyethoxylated and hydrogenated castor oil etc.

With regard to the poloxamers or pluronics suitable as non-ionic surfactants and emulsifiers is referred to the definition given in The Merck Index, 12th edition, 1996 being herewith incorporated by reference. Suitable poloxamers may have an average

mol weight of about 2000 to 12000, preferably 4000 to 10000, more preferred 6000 to 10000, most preferred 8000 to 9000. Examples for specific poloxamers are poloxamer 182LF, poloxamer 331 and poloxamer 188.

- 5 Specific examples of suitable water-soluble diluents are carbohydrates such as monosaccharides like glucose; oligosaccharides like sucrose; and sugar alcohols like erythritol, sorbitol, mannitol, dulcitol, ribitol and xylitol. Mannitol, erythritol, sorbitol and sucrose are preferred diluents.
- 10 The other excipients and/or adjuvants are, for instance, selected from binders, carriers, lubricants, flow control agents, crystallization retarders, solubilizers and coloring agents.

- The binder may be selected from the group of dry binders and/or the group of wet granulation binders, depending on the manufacturing process chosen for the pharmaceutical composition. Suitable dry binders are, e.g., cellulose powder, crystalline cellulose, microcrystalline cellulose or light anhydrous silicic acid. Specific examples of wet granulation binders are corn starch, polyvinyl pyrrolidone (Povidone), vinylpyrrolidone-vinylacetate copolymer (Copovidone) and cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose.
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Suitable disintegrants are, e.g., sodium starch glycolate, Crospovidon, Croscarmellose, sodium carboxymethylcellulose and dried corn starch.

- 25 The other excipients and adjuvants, if used, are preferably selected from diluents and carriers such as cellulose powder, crystalline cellulose or microcrystalline cellulose, cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxy-propylmethylcellulose, dibasic calcium phosphate, corn starch, pregelatinized starch, polyvinyl pyrrolidone (Povidone) etc.; lubricants such as stearic acid, magnesium stearate, sodium stearyl fumarate, glycerol tribehenate, etc.; flow control agents such as colloidal silica, light anhydrous silicic acid, crystalline cellulose, talc, etc.; crystallization retarders such as Povidone,
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(54) **ORAL LIQUID LOSARTAN COMPOSITIONS**

Related U.S. Application Data

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(57) **ABSTRACT**

The present invention is directed to improved oral liquid compositions that include losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier in an amount sufficient to provide a pH of about 6 or higher. Processes of preparing such compositions and methods of administering such compositions are also included.

(21) Appl. No.: **11/493,801**

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embodiment, the phosphate salt concentration is about 80 mM to 120 mM. The losartan, or salt or metabolite thereof, is typically present in an amount of about 1 to 50 mg/mL of the composition.

[0024] In a preferred embodiment, the losartan, or salt or metabolite thereof, is present in an amount of about 8 mg/mL to 20 mg/mL of the composition, and the pharmaceutically acceptable carrier includes a glycol present in an amount of about 5 percent to 25 percent (v/v), glycerin present in an amount of about 20 percent to 40 percent (v/v), a sweetening agent present in an amount of about 0.5 percent to 2 percent (w/v), and a buffering agent present in an amount of about 40 percent to 60 percent (v/v).

[0025] Advantageously, the composition is at least substantially stable. In one embodiment, the degradation of losartan over a period of less than two months is no more than about 1 percent to 2 percent (w/w) at 50° C. In a preferred embodiment, the liquid compositions are substantially stable.

[0026] In an exemplary embodiment, the composition is in solution form.

[0027] The present invention further relates to an oral liquid composition that includes losartan, or a pharmaceutically acceptable salt or metabolite thereof, at least one of propylene glycol or glycerin, along with a sucralose or saccharin-containing component and a phosphate-containing buffer that includes sodium phosphate, potassium phosphate, or a mixture thereof, in an amount sufficient to provide a pH of about 6 or higher.

[0028] The present invention also encompasses stable oral liquid losartan compositions that include losartan or a pharmaceutically acceptable salt or metabolite thereof, a solubilizing agent, a sweetening agent, and a buffering agent, present in an amount sufficient to provide a pH of about 6 or higher over an extended period of time to minimize degradation of the losartan component.

[0029] The present invention additionally includes oral liquid compositions that include solutions of losartan, or a pharmaceutically acceptable salt or metabolite thereof, propylene glycol, glycerin, saccharin sodium, and potassium phosphate buffer, each in an amount sufficient to provide a pH of about 6 or higher.

[0030] The present invention also relates to a method of preparing an oral liquid losartan composition. The method includes dissolving an amount of losartan, or a pharmaceutically acceptable salt or metabolite thereof, into at least one liquid adjuvant to form a liquid losartan solution, and combining the liquid losartan solution with one or more additional pharmaceutically acceptable carriers sufficient to provide a pH of about 6 or higher to form the oral liquid losartan composition. Preferably, the at least one liquid adjuvant includes a buffering agent. The oral liquid losartan composition is typically a clear solution.

[0031] Furthermore, the present invention relates to a method of preventing, treating, or managing hypertension, congestive heart failure, diabetic nephropathy or myocardial infarction in a mammal. The method includes administering to the mammal an effective amount of an oral liquid losartan composition that includes losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one phar-

maceutically acceptable carrier, wherein the oral liquid losartan composition has a pH of about 6 or higher.

[0032] In one embodiment, the composition is administered once or twice a day. In another embodiment, the total daily dose of losartan is from about 25 mg to 100 mg.

[0033] The method preferably also includes administering at least one other therapeutic agent in association with the losartan. The other therapeutic agent(s) typically include another hypertensive agent. The at least one other hypertensive agent generally includes an angiotensin II antagonist, angiotensin converting enzyme inhibitor, or a neutral endopeptidase/angiotensin converting enzyme inhibitor, or a combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] Further features and advantages of the invention can be ascertained from the detailed description that is provided below in connection with the following drawing(s):

[0035] FIG. 1 is a graph showing the solubility profile of losartan as a function of pH;

[0036] FIG. 2 is a graph showing the stability (measured by percent active) of losartan with different buffers at different times;

[0037] FIG. 3 is a graph showing the effect of different concentrations of propylene glycol on the stability of losartan;

[0038] FIG. 4 is a graph showing the stability of losartan (measured by percent active) with different excipient combinations as a function of time;

[0039] FIG. 5 is a graph showing the stability of losartan (measured by percent active) in solutions of propylene glycol, glycerin, and xylitol;

[0040] FIG. 6 is a graph showing the stability of losartan (measured by percent active) with different concentrations of glycerin and at different pHs; and

[0041] FIG. 7 is a graph showing the percent recovery of losartan at different temperatures in different containers.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0042] The present invention provides oral liquid compositions that include losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier in an amount sufficient to provide a pH of about 6 or higher. As used herein, "oral liquid composition(s)" include emulsions, solutions, suspensions, syrups and elixirs, but do not include solid dosage forms that include minor amounts of liquids therein, such as capsules or tablets. Preferably, "oral liquid composition(s)" mean losartan, or a pharmaceutically acceptable salt or metabolite thereof, in solution.

[0043] The present liquid dosage forms provide certain advantages over the solid forms conventionally available. For example, liquid dosage forms are much easier to swallow and typically do not require separate water to administer. Patient compliance is also easier to facilitate with the flavoring and colorant agents that are typically included in

together form about 0.25 weight percent to about 15 weight percent, preferably about 0.4 weight percent to about 10 weight percent, and more preferably about 0.5 weight percent to about 5 weight percent, of the total weight of the composition.

[0054] A thickening agent or viscosity-enhancing agent can be included to generally improve the mouth-feel of the composition and/or to help coat the lining of the gastrointestinal tract. While any suitable thickening agent can be included in the compositions of the present invention, a preferred thickening agent, when used, includes one or more of acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, glycerin, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum. Such a thickening agent, if present, will typically form about 0.1 weight percent to 20 weight percent, preferably about 0.3 weight percent to about 15 weight percent, and more preferably about 0.5 weight percent to 4 weight percent, of the total weight of the composition.

[0055] A sweetening agent, such as one or more of sorbitol, saccharin, sucralose, sodium saccharin, xylitol, sucrose, aspartame, fructose, neotame, sodium saccharate, glycyrrhizin dipotassium, acesulfame K, mannitol, propylene glycol, invert sugar, and mixtures thereof, can be added to modify the taste of the composition. Alternatively or in addition, a viscous sweetener such as one or more of a sorbitol solution, syrup (sucrose solution) glycerin, or high-fructose corn syrup can be used and, in addition to sweetening effects, can also be useful to increase viscosity and to retard sedimentation. Preferably, the sweetening agent includes a saccharin, more preferably sodium saccharin. Such a sweetening agent, if present, will typically be present in an amount sufficient to mask the bitterness of the losartan, or salt or metabolite thereof, and preferably to also mask any other off-flavor components included in the formulation. Typical amounts of sweetening agent include about 0.05 weight percent to about 10 weight percent, preferably about 0.1 weight percent to about 5 weight percent, more preferably about 0.5 weight percent to 2 weight percent, of the total weight of the composition.

[0056] A flavoring agent can enhance patient compliance by making the composition more palatable, particularly in the case of the imbibable compositions of the present invention. The flavoring agent is typically selected in type and amount to decrease or eliminate any bitter taste, i.e., a taste mask, that would otherwise be detectable by the patient to whom the compositions are administered. Examples of a suitable flavoring agent, when used, includes one or more of aspartame, saccharin, menthol, peppermint, anise, and any fruit flavor, such as one or more of grapefruit, orange, lemon, lime, mango, strawberry, pineapple, or cherry; or a combination thereof. A flavoring agent including grapefruit has been found to work especially well according to the invention. The flavoring agent, if present, will typically form about 0.01 weight percent to about 15 weight percent, preferably about 0.5 weight percent to about 10 weight percent, and more preferably about 0.1 weight percent to about 5 weight percent, of the total weight of the composition.

[0057] A colorant agent, when included, can provide the compositions with a more aesthetic and/or distinctive appearance. Colorant agents suitable for inclusion in the present invention include one or more water-soluble synthetic organic food additives (e.g., food dyes such as food red dye Nos. 2 and 3, food yellow dye Nos. 4 and 5 and food blue dye Nos. 1 and 2), water-insoluble lake dyes (e.g., aluminum salts of the above water-soluble synthetic organic food additives, etc.), and natural pigments (e.g., beta-carotene, chlorophyll, iron oxide red, etc.). Suitable colorants include D&C Red No. 33, FD&C Red No. 3, FD&C Red No. 40, D&C Yellow No. 10, and C Yellow No. 6. Such a colorant agent, if present, will typically form about 0.001 weight percent to about 1 weight percent, preferably about 0.005 weight percent to about 0.5 weight percent, and more preferably about 0.0075 weight percent to about 0.25 weight percent, of the total weight of the composition.

[0058] Examples of a suitable preservative component, when used, includes sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole, ethylenediamine tetraacetic acid, paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenylethylalcohol, dehydroacetic acid, sorbic acid, benzalkonium chloride, benzethonium chloride, phenol, phenylmercuric nitrate, thimerosal, and mixtures thereof. A preservative can be added to the compositions at levels safe for ingestion to improve storage stability. A preservative component, if present, will typically form about 0.01 weight percent to about 5 weight percent, preferably about 0.05 weight percent to about 3 weight percent, and more preferably about 0.1 weight percent to about 2 weight percent, of the total weight of the composition.

[0059] The buffering agent preferably included in the liquid compositions can include a buffer solution of one or more gluconate, lactate, citrate, acetate, phosphate, and/or carbonate salts. In addition to providing the about 6 pH or greater, the buffering agent can also modulate drug solubility. Preferably, the buffering agent includes a phosphate, more preferably a potassium phosphate or sodium phosphate buffering agent. Such a buffering agent, if present, will typically form about 10 weight percent to about 80 weight percent, preferably about 30 weight percent to about 70 weight percent, and more preferably about 40 weight percent to about 60 weight percent, of the total weight of the composition.

[0060] Solubilizing and emulsifying agents are used to facilitate more uniform dispersion of an active ingredient or other excipient that is not generally soluble in the liquid carrier. Examples of a suitable emulsifying agent, if used, includes, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, cetyl alcohol, and mixtures thereof. Examples of a suitable solubilizing agent include glycol, glycerin, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, sodium salicylate, sodium acetate, and mixtures thereof. Preferably, the solubilizing agent includes a glycol. Preferred glycols include polyethylene glycol or propylene glycol, or both. The glycol can also act as a stabilizing agent. The solubilizing or emulsifying agent is/are generally present in an amount sufficient to dissolve or disperse the losartan, or salt or metabolite thereof, in the carrier. Typical amounts are from about 1 weight percent to about 80 weight percent, preferably about

container. One sample of each container (except for the stainless steel container) was then stored at 50° C., another one at 40° C. and finally the last sample at room temperature (RT). The stainless steel container was left at room temperature. Samples from each container were then analyzed by HPLC at different times. Table 8 displays the percentage of losartan potassium as a function of time in different containers. The margin of error in the data of the table below is ±0.5%.

TABLE 8

	Temperature (° C.)	0 hours	72 hours	312 hours	1008 hours
Glass Bottle	RT	99.82	99.92	99.80	99.70
Glass Bottle	50	99.82	99.95	99.80	99.90
Glass Bottle	40	99.82	99.92	99.92	99.90
HDPE	RT	99.82	99.92	99.78	99.90
HDPE	50	99.82	99.92	99.80	99.90
HDPE	40	99.82	99.92	99.83	99.90
Brown Glass Bottle	RT	99.82	99.92	99.83	99.90
Brown Glass Bottle	50	99.82	99.92	99.83	99.90
Brown Glass Bottle	40	99.82	99.92	99.83	99.90
Stainless Steel	RT	99.82	99.92	99.83	99.90

[0134] As demonstrated by the data above, the oral liquid losartan composition is stable as a function of time in all the different containers with minimal degradation observed after 1008 hours at room temperature, 40° C. and 50° C. These results demonstrate the superior stability of the losartan potassium in solution and confirm the conclusions of the other studies according to the invention.

[0135] To further confirm these results, the percent recovery of losartan potassium was also measured as a function of time in the different containers. Table 9 and FIG. 7 summarize the results obtained. The margin of error in the data in this table is ±2%.

TABLE 9

	Temperature (° C.)	0 hour	72 hours	312 hours	1008 hours
Glass Bottle	RT	100.00	99.52	99.85	99.04
Glass Bottle	50	100.00	99.93	100.19	99.28
Glass Bottle	40	100.00	99.78	99.91	99.27
HDPE	RT	100.00	100.38	100.42	99.07
HDPE	50	100.00	100.05	100.16	100.22
HDPE	40	100.00	99.51	99.94	99.83
Brown Glass Bottle	RT	100.00	100.00	100.32	99.33
Brown Glass Bottle	50	100.00	100.07	100.38	101.04

TABLE 9-continued

	Temperature (° C.)	0 hour	72 hours	312 hours	1008 hours
Brown Glass Bottle	40	100.00	99.77	100.17	99.15
Stainless Steel	RT	100.00	100.07	100.31	99.49

[0136] Small variations in the percentage of recovery as a function of time were observed in the different containers. In each container at room temperature, there was a small decrease in the recovery percentage of losartan potassium. At less than 1 percent, the decrease, however, was very small. Accordingly, glass bottles, plastic HDPE containers, brown glass bottles, and stainless steel containers are all suitable containers for holding the oral liquid losartan compositions and do not significantly decrease their stability. The preferred form of packaging the liquid formulations of the invention is in PET, HDPE, clear or a brown glass bottle, preferably in a HDPE container.

[0137] Although preferred embodiments of the invention have been described in the foregoing description, it will be understood that the invention is not limited to the specific embodiments disclosed herein but is capable of numerous modifications by one of ordinary skill in the art. It will be understood that the materials used and the chemical or pharmaceutical details may be slightly different or modified from the descriptions herein without departing from the methods and compositions disclosed and taught by the present invention.

What is claimed is:

1. An oral liquid composition comprising losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier in an amount sufficient to provide a pH of about 6 or higher.
2. The composition of claim 1, wherein the pH is about 7 to 10.
3. The composition of claim 2, wherein the pH is about 7.4 to 8.6.
4. The composition of claim 1, wherein the at least one pharmaceutically acceptable carrier comprises one or more of a wetting agent, surfactant component, stabilizing agent, solubilizing agent, thickening agent, sweetening agent, flavoring agent, perfuming agent, colorant agent, preservative agent, or buffering agent.
5. The composition of claim 4, wherein the carrier comprises one or more of a solubilizing agent, a stabilizing agent, a sweetening agent, a flavoring agent effective to mask a bitter taste, or a buffering agent.
6. The composition of claim 5, wherein the carrier comprises a glycol or glycerin, the sweetening agent comprises a sucralose or saccharin-containing component, and the buffering agent comprises a phosphate-containing buffer.
7. The composition of claim 5, wherein the flavoring agent is present and comprises grapefruit, orange, lemon, lime, mango, strawberry, pineapple, cherry, or a combination thereof.
8. The composition of claim 6, wherein the phosphate-containing buffer comprises sodium phosphate, potassium phosphate, or mixtures thereof.

9. The composition of claim 8, wherein the concentration of phosphate salt in the buffering agent is from about 5 mM to 150 mM.

10. The composition of claim 9, wherein the phosphate salt concentration is about 80 mM to 120 mM.

11. The composition of claim 5 wherein the solubilizing agent is present in an amount of about 1 percent to 50 percent (v/v).

12. The composition of claim 5, wherein the sweetening agent is present in an amount of about 0.05 percent to 5 percent (w/v).

13. The composition of claim 5, wherein the buffering agent is present in an amount of about 30 percent to 70 percent (v/v).

14. The composition of claim 6, wherein the glycol is present in amount of about 1 percent to 40 percent (v/v), and the glycerin is present in an amount of about 5 percent to 50 percent (v/v).

15. The composition of claim 1, wherein the losartan, or salt or metabolite thereof, is present in an amount of about 1 to 50 mg/mL of the composition.

16. The composition of claim 1, wherein the losartan, or salt or metabolite thereof, is present in an amount of about 8 mg/mL to 20 mg/mL of the composition, and the pharmaceutically acceptable carrier comprises a glycol present in an amount of about 5 percent to 25 percent (v/v), glycerin present in an amount of about 20 percent to 40 percent (v/v), a sweetening agent present in an amount of about 0.5 percent to 2 percent (w/v), and a buffering agent present in an amount of about 40 percent to 60 percent (v/v).

17. The composition of claim 1, wherein the composition is at least substantially stable.

18. The composition of claim 1, wherein degradation of losartan over a period of less than two months is no more than about 1 percent to 2 percent (w/w) at 50° C.

19. The composition of claim 1, which is in solution form.

20. An oral liquid composition comprising losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one of propylene glycol or glycerin, along with a sucralose or saccharin-containing component and a phosphate-containing buffer comprising sodium phosphate, potassium phosphate, or a mixture thereof, in an amount sufficient to provide a pH of about 6 or higher.

21. A stable oral liquid losartan composition comprising:

losartan or a pharmaceutically acceptable salt or metabolite thereof;

a solubilizing agent;

a sweetening agent; and

a buffering agent, present in an amount sufficient to provide a pH of about 6 or higher over an extended period of time to minimize degradation of the losartan.

22. A oral liquid composition comprising a solution of losartan, or a pharmaceutically acceptable salt or metabolite thereof, propylene glycol, glycerin, saccharin sodium, and potassium phosphate buffer, each in an amount sufficient to provide a pH of about 6 or higher.

23. A method of preparing an oral liquid losartan composition which comprises:

dissolving an amount of losartan, or a pharmaceutically acceptable salt or metabolite thereof, into at least one liquid adjuvant to form a liquid losartan solution; and

combining the liquid losartan solution with one or more additional pharmaceutically acceptable carriers sufficient to provide a pH of about 6 or higher to form the oral liquid losartan composition.

24. The method of claim 23, wherein the at least one liquid adjuvant comprises a buffering agent.

25. The method of claim 23, wherein the oral liquid losartan composition is a clear solution.

26. A method of preventing, treating, or managing hypertension, congestive heart failure, diabetic nephropathy or myocardial infarction in a mammal which comprises administering to the mammal an effective amount of an oral liquid losartan composition comprising losartan, or a pharmaceutically acceptable salt or metabolite thereof, and at least one pharmaceutically acceptable carrier, wherein the oral liquid losartan composition has a pH of about 6 or higher.

27. The method of claim 26, wherein the composition is administered once or twice a day.

28. The method of claim 26, wherein the total daily dose of losartan is between about 25 mg to 100 mg.

29. The method of claim 26, which further comprises administering at least one other therapeutic agent.

30. The method of claim 29, wherein the at least one other therapeutic agent is at least one other hypertensive agent.

31. The method of claim 30, wherein the at least one other hypertensive agent comprises an angiotensin II antagonist, angiotensin converting enzyme inhibitor, or a neutral endopeptidase/angiotensin converting enzyme inhibitor.

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