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(54) Title: IMPROVED PHARMACEUTICAL COMPOSITION OF IBUPROFEN AND METHOD OF MAKING SUCH COMPOSITIONS

(57) Abstract: The active ingredient, ibuprofen or (s)(+)-ibuprofen as free base or as alkali metal salts or mixtures thereof, is covered by this invention in the form of soft gelatin capsule, said soft gelatin capsules have improved soft gelatin capsule gel mass composition which facilitates solubilization of active ingredient. The present invention also proposes the method of producing such a soft gelatin capsule or soft gelatin gel mass composition. One of the further aspects of the present invention is to avoid the use of polyethylene glycol or hydroxide ion species containing solvents as solubilizers for the preparation of soft gelatin capsules containing said active ingredient.

IMPROVED PHARMACEUTICAL COMPOSITION OF IBUPROFEN AND METHOD OF MAKING SUCH COMPOSITIONS

FILED OF THE INVENTION

The present invention relates to the improved pharmaceutical compositions of ibuprofen for enhanced solubilization as soft gelatin capsules. The present invention also proposes the improved soft gelatin capsule gel mass composition to obtain a product with improved solubilization characteristics. One of the further aspects of the present invention is to avoid the use of polyethylene glycol or hydroxide ion species containing solvents as solubilizers for the preparation of soft gelatin capsules containing ibuprofen.

BACKGROUND OF THE INVENTION

Ibuprofen is generally known as Non Steroidal Anti-inflammatory substance having analgesic, anti-inflammatory and antipyretic action. (S)(+)-ibuprofen is pharmacologically active enantiomer of ibuprofen. Patent No. WO 8900421 discloses that administration of only (S)(+) form of ibuprofen instead of racemic ibuprofen represents significant therapeutic advantage.

(R)(-)-ibuprofen is converted in liver to (S)(+)-ibuprofen after absorption from GI tract. The inversion is about 0.69 for (R)(-)-isomer to (S)(+)-isomer of ibuprofen. Total (S)(+) isomer availability from racemate is about 84.5%. Looking at the bioavailability of ibuprofen as (S)(+)-isomer, the racemate results in bioavailability of 70.7% compared to bioavailability of 92.0% for (S)(+)-ibuprofen.

The literature references indicate that the adverse reactions associated with ibuprofen are dose related. The adverse effects associated with ibuprofen are because of comparatively low affinity of ibuprofen for COX-2 receptors than COX-1 receptor.(IC_{50} COX 1/ COX2 = 15). COX-2 is found in low amounts in most healthy tissues except brain and kidney but is expressed only when tissues are inflamed. COX-1 is widely expressed throughout the body and it mediated production of prostaglandin that is essential in the GI tract and platelets. Inhibition of COX-2 is believed to prompt anti-inflammatory, analgesic and antipyretic effect while inhibition of COX-1 can lead to stomach ulceration and other prostaglandin based side effects.

Administration of (S)(+)-ibuprofen results in faster peak plasma concentration (Cmax) resulting in reduced time (Tmax) required to exert therapeutic effect compared to racemic ibuprofen. The

reason is that (S)(+)-ibuprofen is absorbed as such but the contribution from (R)(-)-ibuprofen comes only after its conversion to (S)(+)-ibuprofen.

(S)(+)-ibuprofen being active form is advantageous in hepatic compromised patients. In liver diseases conditions like liver cirrhosis the conversion of (R)- form to (S) form is impaired and only 50% of racemic dose as (S)(+)-ibuprofen is available which may not be sufficient to bring about effective therapeutic effect.

As disclosed in U.S. Pat. No. 5,560,926 there are some disadvantages of (S)(+)-ibuprofen due to its physical nature as far as the formulation is concerned. The melting point of (S)(+)-ibuprofen is very low at 52°C, while the racemate melts at 75°C. This makes conventional granulation technique in the production of granules almost impossible since owing to addition of heat, which is necessary during drying the active compound starts to melt or sinters.

Patent No. ES-OS 0299668 describes the production of hard gelatin capsules by filling with melts. Melt embedded materials pose a problem of crystal modification and altered bioavailability. Also this type of dosage form is not suitable for rapid releasing form but generally is intended to give sustained release form.

Patent No. WO 8802625 describes the production of soft gelatin capsule, which is filled with dissolved raw ibuprofen. In this case ibuprofen is dissolved in polyethylene glycol and further solubility is enhanced by neutralizing the ibuprofen with KOH. This type of administration, however, is not suitable for (S)(+)-ibuprofen, since either undesirable high decrease in content generally occur as a result of esterification reactions of (S)(+)-Ibuprofen with alcohol in this type of solution of active compound or else racemization of (S)(+)-ibuprofen occur as a result of addition of KOH.

It is difficult to dissolve ibuprofen in solvent volume small enough to produce softgel that is appropriate from the standpoint of economics and patient acceptance. Water, glycerin, low molecular weight alcohols, ketones, acids, amines and esters are unsuitable as fill material for softgel. Presence of water above 20% may dissolve soft gelatin capsule shell.

Mortan et al., U.S. Pat. No. 5,376,688 discloses the preparation of pharmaceutically accepted solution of acidic, basic and amphoteric pharmaceutical agent suitable for encapsulation in

gelatin capsule for subsequent oral administration and include pharmaceutical agent, an ion species and solvent system. Unlike Mortan who uses hydroxide ion species to carry out the ionization of acidic pharmaceutical agent, the present investigation uses alkali metal bicarbonate to carry out partial ionization of ibuprofen and subsequent conversion into alkali metal salt. Potassium hydroxide and other hydroxide ion species containing agents are avoided in the present invention, instead alkali metal bicarbonate is used for the partial or complete conversion of ibuprofen into its alkali metal salts. Moreover, use of potassium bicarbonate facilitates the conversion of ibuprofen to potassium ibuprofen with the help of the evolved carbon dioxide in the above reaction, which is referred as gas powered technique of solubilization in this specification and in the appended claims.

Yu et al., U.S. Pat. No. 5,360,615 teaches the use of polyvinyl pyrollidone, polyethylene glycol and propylene glycol to enhance the solubility of acidic pharmaceutical agent. The invention of Yu et al., neither teaches nor describes the use of Labrasol to enhance the solubility of acidic pharmaceutical agent. Moreover, the present invention avoids the use of polyethylene glycol as solvent for solubilizing ibuprofen or (S)(+)-ibuprofen before filling into softgels as polyethylene glycol is not suitable fill material/solvent for (S)(+)-ibuprofen. It is reported in the prior literature that the use of polyethylene glycol in the formulation of (S)(+)-ibuprofen causes undesirable high decrease in content due to esterification or the racemization of (S)(+)-ibuprofen.

Yu et al. al. U.S. Pat. No. 5,071,643 describes the solvent system enhancing the bioavailability of the acidic pharmaceutical agent. Yu et al. invention consists of use of hydroxide ions to carry out the partial ionization of the acidic pharmaceutical agent and use of solvent system containing polyvinyl pyrollidone, and polyethylene glycol to enhance the bioavailability of acidic pharmaceutical agent. The present invention differs from Yu et al. as it is free of polyvinyl pyrollidone or polyethylene glycol and present invention uses different process of carrying out partial ionization of ibuprofen. In the present invention gas powered technique utilizing alkali metal bicarbonate is used to carry out the partial ionization of ibuprofen. Moreover, the use of polyethylene glycol as suggested by U.S. Pat. No. 5,071,643 is not suitable for the formulation of (S)(+)-ibuprofen.

It is important to note that non aqueous medium is preferred choice as fill medicaments during soft gelatin capsule manufacturing, as they do not imbibe water from wet gelatin ribbons. However to have a rapidly dissolving formulation the fill material should be easily dispersible in

aqueous media. Labrasol possess both these characteristics due to its amphiphilic nature. It aids the solubilization of poorly water-soluble drugs and subsequent dispersion in gastric fluid by forming a microemulsion, which produces large surface area for the faster and uniform absorption of active ingredient. Absorption of drug solubilized in Labrasol is generally not affected by the presence or absence of food in stomach.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to obtain an improved pharmaceutical composition containing ibuprofen or (S)(+)-ibuprofen as free base or as alkali metal salt thereof, suitable to be incorporated into soft gelatin capsules.

It is another object of the present invention to solubilize (S)(+)-ibuprofen in Labrasol, Transcutol or mixtures thereof, and thus avoid the use of polyethylene glycol or other hydroxide ion containing agents as soft gelatin fill material.

It is still another object of the present invention to develop a improved composition of soft gelatin capsule gel which further improves the characteristics of the product.

DETAILED DESCRIPTION OF THE INVENTION

Present invention overcomes the problem of retardation of active ingredient from the capsule composition. The invention also presents the solvents for improved solubilization of (S)(+)-ibuprofen while avoiding the use of polyethylene glycol as solvent.

Published literature and patents support the fact that after exposure of gelatin capsule to higher temperatures and humidity under accelerated stability studies, as per the ICH guidelines, causes retardation in dissolution of capsule, which subsequently affects its bioavailability. One of the accepted mechanism for this retardation of dissolution is crosslinking of gelatin due to reaction of aldehyde, which is present either in capsule excipients or as a part of gelatin capsule shell, with the amino acids present in gelatin of capsule shell. Modification of soft gelatin capsule shell is therefore necessary in order to avoid such problem. It is noteworthy that such modification largely depends on the physicochemical characteristics of the product to be incorporated into soft gelatin capsule.

As used in this specification and in the appended claims the term active ingredient refers to ibuprofen or (S)(+)-ibuprofen as free base or as alkali metal salt or mixtures thereof. When the active ingredient is (S)(+)-ibuprofen, it is not necessary to convert it to its alkali metal salt, however when the active ingredient is ibuprofen it should be converted into its alkali metal salt either partially or completely in order to obtain better solubilization as per this invention.

As used in this specification and in the appended claims the term "gas powered solubilization technique" means the process of conversion of ibuprofen or (S)(+)-ibuprofen into its cationic salt by adding the alkali metal bicarbonate as dry powder or as aqueous solution, in Labrasol, Transcutol, or mixtures thereof, containing the active ingredient. Alternatively, the active ingredient and alkali metal salt can also be added to Labrasol, Transcutol or mixtures thereof. The said mixture may optionally contain amino acids depending on the intended final product as per this invention. There may be partial or complete conversion of active ingredient to its alkali metal salt by the above mentioned process of gas powered solubilization technique.

In this specification and in the appended claims the term Transcutol means Transcutol P, which is chemically Diethylene Glycol Monoethyl Ether, procured from Gattefosse, France. Labrasol is chemically Caprylocaproyl Macrogol-8 Glycerides, procured from Gattefosse, France.

The term "metal ion carbonate" used in this specification and in the appended claims means carbonates selected from any of the metals from sodium, lithium or potassium, more preferably potassium. Soft gelatin capsule has its conventional meaning (soft elastic gelatin capsule or softgel).

The term improved solubilization used in this specification and in the appended claims means the increased solubility of active ingredient, which increases the bioavailability of the active ingredient from soft gelatin capsule.

The solvent means any of the ingredients, without active ingredient, selected from Labrasol, vegetable oils, glycin or mixtures thereof. The term "hydroxide ion containing solvent" means the solvents/vehicles/capsule fill materials, used to fill soft gelatin capsule, which have high free hydroxyl value like methanol, ethanol, polyethylene glycol etc. The words solvents, vehicles or capsule fill material are used interchangeably in this specification. Unless otherwise specified Anidrisorb is anidrisorb 85/70 which is aqueous solution of D-sorbitol and sorbitans, supplied by

Roquette, France. Sorbitol special solution is aqueous sorbitol and sorbitol and sorbitol anhydrides, supplied by SPI Pharma., France. The Labrasol or Transcutol of the present invention may be replaced with any of the solvents selected from the group consisting of coconut oil; corn oil; olive oil; palm oil; peanut oil; safflower oil; sesame oil; soybean oil; hydrogenated castor oil; hydrogenated coconut oil; partially hydrogenated soybean oil; glyceryl tricaprate; glyceryl trilaurate; glyceryl trioleate; glyceryl trilinoleate; glyceryl tricaprylate/caprate; glyceryl tricaprylate/caprate/laurate; glyceryl tricaprylate/caprate/linoleate; glyceryl tricaprylate/caprate/stearate; saturated polyglycolized glycerides (Gelucire 44/14, Gelucire 14 50/13 and Gelucire 53/10); linoleic glycerides (Maisine 35-I); and caprylic/capric glycerides (Imwitor 742) or other pharmaceutically accepted surfactants.

Unless otherwise specified the term "pharmaceutical composition' as used in this specification and in the appended claims means soft gelatin capsule fill material with the active ingredient ready to be filled into soft gelatin capsule. The soft gelatin gel mass as used in this specification and in the appended claims refers to mixture of ingredients, which make the soft gelatin shell.

The word "incorporat(ed)" as used in this specification and in the amended claims refers to filling of soft gelatin capsule with pharmaceutical composition according to present invention.

The amino acids are selected from the group consisting of glycine, tryptophan, lysine, leucine, threonine, aspartic acid, glutamic acid, asparagine, glutamine, lysine, arginine, cysteine, phenylalanine, tyrosine, histidine, acetylcysteine, valine, alanine, isoleucine, ornithine, p-aminobenzoic acid, nicotinic acid, or a salt thereof.

The carboxylic acids are selected from the groups consisting of benzoic acid, fumaric acid, maleic acid, citric acid, ascorbic acid, edetic acid, lactic acid, sorbic acid, tartaric acid, adipic acid, succinic acid, gluconic acid, or a salt thereof.

The pH of the composition before filling into softgel is in the range of 2.5 to 7.5. The temperature should be in the range of 25-65^{O}C to carry out the conversion of ibuprofen or (S)(+)-ibuprofen into its alkali metal salt form.

In an effort to obtain the soft gelatin capsule containing active ingredient with Labrasol, Transcutol or mixtures thereof, it was observed that there is a retardation of the dissolution of active ingredient in acidic media as per the dissolution carried out by USP method.

Example 1.

Soft gelatin capsule gel mass composition

Ingredients	Quantity taken (in percentages)
Gelatin	43.77
Glycerin	11.63
Sorbitol	4.98
FDC green No. 3	0.006
Methyl paraben	0.18
Propyl paraben	0.02
Purified water	39.40

Composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Labrasol	200
Potassium bicarbonate	29.1
Purified water	29.1

Example 2.

Soft gelatin capsule gel mass composition

As described in example 1.

Composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Ingredients	Quantity taken (in mg)
Labrasol/ Transcutol	200
Sodium bicarbonate	29.1
Purified water	29.1

It was surprisingly observed that addition of glycin or other amino acids in the above composition improved the solubilization of active ingredient from the product, said composition is called as improved composition in this specification.

Example 3.

Soft gelatin capsule gel mass composition

Ingredients	Quantity taken (in percentages)
Gelatin	43.77
Glycerin	11.63
Sorbitol	4.98
FDC green	0.006
Methyl paraben	0.18
Propyl paraben	0.02
Purified water	39.40

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Labrasol	265
Glycin	1.31
Potassium bicarbonate	29.1
Purified water	40.1

Example 4.

Soft gelatin capsule gel mass composition

As described in example 3.

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Transcutol	265
Glycin	1.31
Potassium bicarbonate	29.1
Purified water	40.1

In order to further improve the dissolution of above improved composition, changes were tried in the soft gelatin capsule gel mass composition, said gel mass composition is called as improved gel mass composition in this specification.

Example 5.

Improved soft gelatin capsule gel mass composition

Ingredients	Quantity taken (in percentages)
Gelatin	43.12
Glycerin	11.47
Sorbitol solution	4.91
Glycin	0.98
Citric acid	0.49
FDC green ND-3	0.0059
Methyl paraben	0.18
Propyl paraben	0.02
Purified water	38.82

Composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Labrasol/ Transcutol	200
Potassium bicarbonate	29.1
Purified water	29.1

Example 6.

Improved soft gelatin capsule gel mass composition

As described in example 5.

Composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
(S)(+)-ibuprofen	200
Labrasol/ Transcutol	200

It was further noticed that with further addition of sorbitol special solution and anidrisorb into this improved gel mass composition, which is called final improved gel mass composition, the resulting final product, in the form of soft gelatin capsule, shows better dissolution, stability and physicochemical characteristics.

Example 7.

Final improved soft gelatin capsule gel mass composition

Ingredients	Quantity taken (in percentages)
Gelatin	43.59
Sorbitol special solution	8.28
Anidrisorb 85/70	8.28
FDC green	0.006
Methyl paraben	0.18
Propyl paraben	0.02
Purified water	39.64

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Labrasol/Transcutol	265
Glycin/glutamic acid	1.31
Potassium bicarbonate	29.1
Purified water	40.1

Example 8.

Improved soft gelatin capsule gel mass composition

As described in example 7.

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Labrasol /Transcutol	265

Ingredients	Quantity taken (in mg)
Glycin/alanine	1.31
Potassium bicarbonate	29.1
Purified water	40.1

Example 9.

Improved soft gelatin capsule gel mass composition

As described in example 7.

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Labrasol /Transcutol	265
Sodium bicarbonate	29.1
Purified water	40.1

Example 10.

Improved soft gelatin capsule gel mass composition

As described in example 7.

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
Ibuprofen	200
Transcutol	260

Example 11.

Improved soft gelatin capsule gel mass composition

As described in example 7.

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
(S)(+)-ibuprofen	200
Transcutol	260

Example 12.

Improved soft gelatin capsule gel mass composition

As described in example 7.

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
(S)(+)-Ibuprofen	200
Labrasol/Transcutol	265
Glycin/arginine	1.31
Potassium bicarbonate	29.1
Purified water	40.1

Example 13.

Improved soft gelatin capsule gel mass composition

As described in example 7.

Improved composition to be incorporated in soft gelatin capsule

Ingredients	Quantity taken (in mg)
(S)(+)-Ibuprofen	200
Labrasol	200

Preparation method of soft gelatin capsule:

1. Labrasol is taken in suitable container and heated at temperature ranging from 25^0C–65^0C.
2. Alkali metal bicarbonate is dissolved in purified water and heated to 25^0C–65^0C. Weighed quantity of active ingredient and alkali metal bicarbonate as dry powder or as aqueous solution, is slowly added to the said Labrasol/Transcutol solution by constant stirring at 100-5000 rpm.
3. The resulting solution is cooled to room temperature and incorporated in soft gelatin capsules.

The Labrasol as per step 1, can be mixed or replaced by Transcutol, glycin or mixture thereof. The alkali metal carbonate can be selected bicarbonates of sodium, lithium or potassium metals.

Many modifications in the above method can be done based on the convenience of the operator and ingredients used.

Above examples are meant to be explanatory only and should not be construed to limit the scope of the invention in any way. Many modifications in the above invention are obvious to those skilled in the art and are contemplated to be within the scope of the appended claims.

We Claim:

1. A pharmaceutical composition in the form of soft gelatin capsule comprising, an active ingredient, Labrasol, Transcutol or mixtures thereof optionally containing amino acids.
2. The composition of claim 1 wherein, the active ingredient is selected from ibuprofen, (S)(+)-ibuprofen or mixtures thereof.
3. The composition as in any of claims 1-2 wherein, the active ingredient is in the range of, from about 20% to about 60%, preferably from 30% to about 45%, of the total composition.
4. The composition of claim 1 comprising Labrasol, Transcutol or mixtures thereof, in the range of from about 20% to about 60%, preferably from about 30% to about 45% of the total composition.
5. The composition as in any of claims 1-4 comprising at least one amino acid selected from glycine, tryptophan, lysine, leucine, threonine, aspartic acid, glutamic acid, asparagine, glutamine, arginine, cysteine, phenylalanine, tyrosine, histidine, acetylcysteine, valine, alanine, isoleucine, ornithine, p-aminobenzoic acid, nicotinic acid, or a salt thereof.
6. The composition as in any of claims 1-5 wherein the active ingredient is converted to its alkali metal salt by gas powered solubilization technique using alkali metal carbonates.
7. The composition of claim 6 wherein alkali metal carbonate is selected from any of potassium bicarbonate, sodium bicarbonate or lithium bicarbonate, preferably potassium bicarbonate.
8. The composition of claim 7 wherein alkali metal bicarbonate is in the range of from about 0.05 to about 0.8 mole per mole of active ingredient more preferably from about 0.1 mole to 0.5 moles per mole of active ingredient.
9. The composition as claimed in claim 1, comprising soft gelatin gel mass consisting of gelatin, sorbitol special solution, anidrisorb, amino acids and carboxylic acids.
10. The composition of claim 9 comprising gelatin from about 30% to about 60%, sorbitol special from about 5% to about 30%, anidrisorb from about 5% to about 30% and water from about 25% to about 50%.
11. The composition as in any of claims 9-10 wherein the amino acid comprises one or more of glycine, tryptophan, lysine, leucine, threonine, aspartic acid, glutamic acid, asparagine, glutamine, arginine, cysteine, phenylalanine, tyrosine, histidine, acetylcysteine, valine, alanine, isoleucine, ornithine, p-aminobenzoic acid, nicotinic acid, or a salt thereof

12. The composition as in any of claims 9-10 wherein the carboxylic acid comprises one or more of benzoic acid, fumaric acid, maleic acid, citric acid, ascorbic acid, edetic acid, lactic acid, sorbic acid, tartaric acid, adipic acid, succinic acid, gluconic acid, or a salt thereof.

13. The composition as in any of claims 9-12 comprising at least glycin as amino acid and citric acid as carboxylic acid.

14. The composition of claim 13 comprising glycin in the range of form about 0.1% to about 1%.

15. The composition of claim 13 comprising citric acid in the range of form about 0.1% to about 1%.

16. A method of making soft gelatin capsule comprising:

(a) adding a alkali metal carbonate, as a dry powder or as an aqueous solution, to Labrasol, Transcutol or mixture thereof optionally containing amino acid wherein said Labrasol, Transcutol or mixture thereof, contains at least one active ingredient; or,

(b) adding an active ingredient to Labrasol, Transcutol or mixture thereof optionally containing amino acid; or,

(c) adding all the ingredients in (a) or (b) simultaneously or consecutively.

17. A method of making soft gelatin capsule comprising:

(a) dispersing glycin as dry powder or as aqueous solution, to Labrasol, Transcutol or mixtures thereof;

(b) adding the active ingredient as dry powder or in aqueous form, in the mixtures of step (a)

wherein alkali metal bicarbonate is optionally added in either step (a) or step (b), preferably in step (b).

18. The method of any of claims 16 or 17 wherein, the active ingredient comprises any of ibuprofen, (S)(+)-ibuprofen or mixtures thereof.

19. The method as in any of claims 16-18 wherein, the active ingredient ranges from about 20% to about 60 %, preferably from 30% to about 45%.

20. The method of any of claims 16 or 17 comprising Labrasol, Transcutol or mixtures thereof, from about 20% to about 60 %, preferably from about 30 to about 45%.

21. The method of any of claims 16-19 comprising at least one amino acid from the group consisting of glycine, tryptophan, lysine, leucine, threonine, aspartic acid, glutamic acid, asparagine, glutamine, arginine, cysteine, phenylalanine, tyrosine, histidine,

acetylcysteine, valine, alanine, isoleucine, ornithine, p-aminobenzoic acid, nicotinic acid, or a salt thereof

22. The method of claim any of claims 16-19 comprising at least one carboxylic acid from the group consisting of benzoic acid, fumaric acid, maleic acid, citric acid, ascorbic acid, edetic acid, lactic acid, sorbic acid, tartaric acid, adipic acid, succinic acid, gluconic acid, or a salt thereof.

23. A method of treating mammalian organism in need of such treatment comprising administering to said mammalian organism the composition as in any of claims 1-22.