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(54) Benævnelse: **SAMMENSÆTNINGER OMFATTENDE POLYETHYLENGLYCOL OG ALKALIMETAL- ELLER**

Fortsættes ...

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DESCRIPTION

[0001] The present invention relates to a method of cleansing the colon using colon cleansing solutions, and compositions and kits associated therewith. Colon cleansing compositions are also known as lavage solutions, bowel cleansers, purgatives or colonic evacuants.

1. Background

[0002] Colon or bowel cleansing is important before numerous surgical or diagnostic procedures, including colonoscopy, barium enema examination, sigmoidoscopy and colon surgery. Such procedures are often carried out on an outpatient basis and thus it is desirable that the colon cleansing be carried out by the patient at home, prior to arrival at the hospital or surgery where the procedure is to take place. It is therefore important that patient compliance is good without medical supervision if satisfactory colon cleansing is to be achieved prior to the procedure.

[0003] Intestinal lavage, in which a large volume of an aqueous electrolyte solution containing sodium sulphate and polyethylene glycol is ingested, is one of the most common methods for colon cleansing. These osmotically active agents are non-absorbable or only poorly absorbable and thus retain water in the bowel, resulting in copious diarrhoea and cleansing of the colon.

[0004] For effective cleansing, many of these compositions must be ingested in quantities of between 2 to 4 litres. The unpleasant taste of these compositions combined with the large volumes required to be ingested often contributes to nausea or vomiting, resulting in poor patient compliance and failure to consume the full volume of solution. Poor patient compliance can lead to inadequate preparation of the colon which can, in turn, lead to cancellation or repetition of the colonoscopy becoming necessary or, worse, non-detection of lesions or polyps indicative of cancer risk.

[0005] A number of improved colon cleansing compositions are described in WO 2004/037292. A colon cleansing composition according to WO 2004/037292 that comprises polyethylene glycol 3350, sodium sulphate, an ascorbate component, electrolytes, sweetener and flavouring is commercialised as a powder for oral solution under the tradename MOVIPREP® (registered trademark of Velinor AG, a member of the Norgine group of companies). The MOVIPREP solution is effective despite being taken in a substantially lower volume than other colon cleansing solutions. Typically, only 2 litres of the solution need to be taken by an adult patient (along with additional clear fluid), a significant benefit when compared to taking 4 litres of previous solutions.

[0006] A recent advance in colon cleansing agents is provided by the product marketed as

SUPREP by Braintree Laboratories, Inc. SUPRPEP contains 17.5g sodium sulphate, 3.13g potassium sulphate and 1.6g magnesium sulphate and it is taken in a volume of 16 US fluid ounces (473ml). A treatment comprises two doses of that solution.

[0007] Various regimens for the timing of ingestion of colon cleansing solutions are mentioned in the literature and in patient information leaflets that accompany colon cleansing products. For example, the MOVIPREP solution mentioned above may be taken (optionally with additional clear liquids also being taken) in the evening before the examination or procedure, or the MOVIPREP solution may be taken in a "split-dose" regimen, with approximately half of the cleansing solution being taken the evening before the examination or procedure ("first dose"), and the remainder being taken the following morning ("second dose"). Similarly, the SUPREP product mentioned above is recommended to be taken as first dose in the evening before the examination procedure, accompanied by an additional quart of water (946ml), followed by a second dose in the morning of the procedure.

[0008] An alternative to the lavage solutions described above is provided by low volume hypertonic salt solutions. Examples include Fleet's phosphosoda product and sodium picosulphate solutions. These are very concentrated salt solutions and patients need ingest only a small volume of them (around 100ml). However, these products have been associated with a hypo-osmolar state and electrolyte imbalance in subjects, particularly hyponatremia. They are particularly counter-indicated in subjects with kidney problems.

[0009] Despite the advances that have been made, all lavage-type colon cleansing products on the market continue to require a subject to ingest a large volume of solution (2 litres in the case of the MOVIPREP solution). Many subjects find the ingestion of a large volume unpleasant or difficult and poor patient compliance thus remains a problem. There remains a need for alternative colon cleansing solutions that are effective when ingested in small volumes, but do not cause electrolyte imbalances in subjects. There also remains a need for colon cleansing solutions that are more pleasant to subjects to ingest, whilst retaining good cleansing effectiveness.

2. Summary

[0010] In a first aspect, there is provided a first colon cleansing solution comprising:

1. (i) 175 to 225 g per litre PEG having an average molecular weight of 2500 to 4500 Da;
2. (ii) 17 to 19 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;
3. (iii) optionally one or more electrolytes;
4. (iv) optionally one or more flavouring agents; and
5. (v) optionally one or more sweeteners.

[0011] Furthermore, there is provided a kit comprising:

- a first colon cleansing solution, and
- a second colon cleansing solution,

wherein the first colon cleansing solution is as described herein and the second colon cleansing solution comprises:

1. a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of:
    1. (i) ascorbic acid and
    2. (ii) one or more salts of ascorbic acid
       the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0; and
2. b) 10 to 200 g per litre polyethylene glycol.

[0012] The second colon cleansing solution has a surprisingly palatable taste. The particular ratio of ascorbic acid to salt of ascorbic acid enables the salty taste of ascorbate salt to be balanced by sourness from acid to a palatable extent, whilst at the same time not reducing the osmotic effect of the ascorbate component or making the solution too sour. The solution is highly effective as a colon cleansing solution when ingested in a lower volume than many prior art solutions, and it has a good tolerability profile.

[0013] There is also provided a kit of the invention for use in a method of cleansing the colon comprising:

- the subject taking an effective amount of a first colon cleansing solution as described herein; and then
- the subject taking an effective amount of a second colon cleansing solution as described herein.

3. Detailed description

a) Contents of solutions

[0014] The solutions of the invention are aqueous solutions. The mixture of ascorbic acid and one or more salts of ascorbic acid will, for convenience, be referred to herein as the "ascorbate component". Suitable salts of ascorbic acid include alkali metal salts and alkaline earth metal salts. For example, a salt may be selected from sodium, potassium, magnesium and calcium salts. For example, preferred salts of ascorbic acid include sodium ascorbate, potassium

ascorbate, magnesium ascorbate and calcium ascorbate. The molar ratio between (i) the ascorbic acid and (ii) the one or more salts of ascorbic acid is the molar ratio of the ascorbate moieties; for example, magnesium ascorbate comprises two moles of ascorbate per mole of salt; for the ratio purposes, it is the number of moles of ascorbate that is counted. Particularly preferred salts of ascorbic acid are magnesium ascorbate and sodium ascorbate, for example sodium ascorbate. In one embodiment, the solution comprises ascorbic acid and sodium ascorbate (and preferably no further ascorbate).

[0015] Preferably, the molar ratio of the components (i) and (ii) is from 1:4.75 to 1:6.75; more preferably from 1:5.0 to 1:6.0; for example from 1:5.40 to 1:5.80; for example 15:85.

[0016] The second solution preferably comprises ascorbate anion in a concentration of: 300-700mmol per litre, for example 350-650mmol per litre, for example 450-600 mmol per litre.

[0017] A second solution may comprise 50 to 140g/litre of ascorbate component. For example, a solution comprises 60 to 140g/litre, for example 80 to 130g/litre, for example 80 to 120g/litre, for example 100 to 120g/litre of ascorbate component.

[0018] Ascorbic acid has a molecular weight of 176g/mol. Sodium ascorbate has a molecular weight of 198g/mol. Accordingly, a mixture of ascorbic acid and sodium ascorbate in a molar ratio of from 1:4.5 to 1:7.0 has ascorbic acid and sodium ascorbate present in a weight ratio of 1:5.063 to 1:7.875. For example, the weight ratio can be 1:5.344 to 1:7.594; more preferably from 1:5.625 to 1:6.75; for example from 1:6.075 to 1:6.525, for example 1:6.38. For example, a solution may comprise from 6 to 25 g/litre of ascorbic acid and 50 to 120 g/litre of sodium ascorbate, for example 12 to 20 g/litre of ascorbic acid and 80 to 120 g/litre of sodium ascorbate (with the ratio between them being as mentioned above). For example, a solution may comprise from 14 to 16g g/litre of ascorbic acid and 92 to 100 g/litre of sodium ascorbate.

[0019] Potassium ascorbate has a molecular weight of 214g/mol. Accordingly, a mixture of ascorbic acid and potassium ascorbate in a molar ratio of from 1:4.5 to 1:7.0 has ascorbic acid and potassium ascorbate present in a weight ratio of 1:5.471 to 1:8.511. For example, the weight ratio can be 1:5.776 to 1:8.208; more preferably from 1:6.080 to 1:7.295; for example from 1:6.565 to 1:7.052, for example 1:6.896. For example, a solution may comprise from 6 to 25 g/litre of ascorbic acid and 50 to 125 g/litre of potassium ascorbate, for example 6 to 12 g/litre of ascorbic acid and 80 to 120 g/litre of potassium ascorbate.

[0020] Magnesium ascorbate has a molecular weight of 374.5g/mol and each mole of magnesium ascorbate provides two moles of ascorbate. Accordingly, a mixture of ascorbic acid and magnesium ascorbate in a molar ratio of from 1:4.5 to 1:7.0 (of ascorbate anion) has ascorbic acid and magnesium ascorbate present in a weight ratio of 1:4.794 to 1:7.457. For example, the weight ratio can be 1:5.061 to 1:7.191; more preferably from 1:5.326 to 1:6.397 for example from 1:5.753 to 1:6.179, for example 1:6.042. For example, a solution may comprise from 6 to 25 g/litre of ascorbic acid and 45 to 120 g/litre of magnesium ascorbate, for example 6 to 12 g/litre of ascorbic acid and 75 to 115 g/litre of magnesium ascorbate.

[0021] Depending on the pH of the solution, some ascorbate anion may be protonated and thus exist as free ascorbic acid in solution. At the pH of solutions that would typically be administered, only a very minor proportion of ascorbate is protonated. In calculations of concentrations of "ascorbate anion" herein, the concentration of "ascorbate anion" is taken as the total concentration of all ascorbate anion present, including the proportion that is protonated.

[0022] The second cleansing solution comprises polyethylene glycol. The polyethylene glycol (PEG) may, for example, have an average molecular weight of 2000 to 8000, for example 2500 to 4500 Da, for example 2680 to 4020 Da, for example 3000 to 4000 Da. For example, the PEG may be PEG 3350 or PEG 4000 as defined in national pharmacopeias. PEG8000 may also be used. Further examples of suitable PEGs recognized in some national pharmacopeias include Macrogols, for example Macrogol 3350 or Macrogol 4000.

[0023] The second cleansing solution comprises 10 to 200 g per litre of PEG. Preferably, the solution comprises 20 to 160g per litre of PEG, more preferably 40 to 120 g per litre, for example 60 to 100 g per litre, for example 75 to 85 g per litre, for example 80 g per litre.

[0024] The second cleansing solution may additionally comprise one or more of:

c) one or more electrolytes;

d) one or more alkali metal or alkaline earth metal sulphates;

e) one or more flavouring agents;

f) one or more sweeteners.

[0025] The second cleansing solution may comprise one or more electrolytes. Electrolytes include salts of sodium, potassium, calcium and magnesium, particularly sodium and potassium; and salts of chloride, iodide, bicarbonate and carbonate, particularly chloride. Preferred electrolytes are sodium chloride and potassium chloride. In an embodiment, the solution is essentially free from sodium bicarbonate, for example essentially free from any bicarbonate.

[0026] For example, the second solution may comprise sodium chloride at a concentration of 1 to 10 g per litre. For example, sodium chloride may be present at a concentration of 3 to 8 g per litre, for example 4 to 7g per litre; for example 6.0 to 6.8g per litre; for example 5.6g per litre or 6.4g per litre.

[0027] For example, the second solution may comprise potassium chloride at a concentration of 1 to 10 g per litre. For example, potassium chloride may be present at a concentration of 1 to 7 g per litre, for example 1.5 to 5g per litre, for example 1.5 to 3g per litre, for example 2.0 to

2.8 g per litre; for example 2.4g per litre or 2.6g per litre.

[0028] In an embodiment, the second solution comprises sodium chloride and potassium chloride. They can be present in the amounts mentioned immediately above. For example, sodium chloride may be present at a concentration of 4 to 7g per litre and potassium chloride may be present at a concentration of 1.5 to 3g per litre.

[0029] In the solutions of the invention described herein, the quantities of the individual components recited do not include any solutes that may be present in the water used to prepare the solutions, for example, in hard water areas there may be significant amounts of Ca^{2+} and Mg^{2+} carbonates, bicarbonates or sulphates present in tap water.

[0030] The second cleansing solution preferably includes a flavouring agent. A flavouring for use in compositions of the invention should preferably mask saltiness, be relatively sweet but not excessively so, and be stable in the composition. A flavouring makes the solutions more palatable and thus aids patient compliance. Preferred flavourings include lemon e.g. Ungerer Lemon (available from Ungerer Limited, Sealand Road, Chester, England CH1 4LP), strawberry e.g. Ungerer Strawberry, grapefruit e.g. Ungerer Grapefruit flavouring powder, blackcurrant e.g. Ungerer Blackcurrant, pineapple e.g. IFF (International Flavours and Fragrances) Pineapple flavouring powder, orange eg Firmenich Orange, vanilla/lemon and lime e.g. IFF Vanilla and Givaudin Roure Lemon and Lime Flav-o-lok, fruit punch eg Ungerer fruit punch, citrus punch, mango, and berry. Those and further suitable flavourings are available from International Flavours and Fragrances Inc. (Duddery Hill, Haverhill, Suffolk, CB9 8LG, England), Ungerer & Company (Sealand Road, Chester, England CH1 4LP) or Firmenich (Firmenich UK Ltd., Hayes Road, Southall, Middlesex UB2 5NN). More preferred flavourings are lemon, kiwi, strawberry, grapefruit, orange, fruit punch and mango. Citrus flavour, orange grapefruit flavour and orange flavour are particularly preferred.

[0031] The amount of flavouring required depends on the nature and strength of the flavouring in question. Typically, it is 0.05 to 4.5 g per litre, for example 0.05 to 2.0 g per litre, for example 0.2 to 1.8g per litre, for example 1.0 to 1.8g per litre, for example 3.0 to 4.5g per litre, for example 0.3g per litre or 1.2g per litre, for example 3.2 or 4.2g per litre.

[0032] The second cleansing solution preferably includes a sweetener. Sugar-based sweeteners are generally not suited for colon cleansing compositions because the delivery of unabsorbed sugars to the colon provides a substrate for bacteria. Such sugars may be metabolised by the bacteria to form explosive gases such as hydrogen and methane. The presence of explosive gases in the colon can be highly dangerous when electrical apparatus is to be used during colonoscopy or other procedures. Preferred sweeteners include aspartame, acesulfame potassium (acesulfame K), sucralose and saccharine, and/ or combinations thereof. For example, compositions of the invention may comprise one or both of aspartame and acesulfame potassium (acesulfame K). For example, compositions of the invention may comprise one or both of sucralose and acesulfame potassium (acesulfame K). In a preferred embodiment, the solution comprises aspartame or sucralose, for example aspartame.

[0033] Alternatively, compositions of the invention can be essentially free from added sweeteners, for example to minimize the number of different components in the compositions.

[0034] A souring agent (for example citric acid) may be present as a taste enhancer. A souring agent is a component that imparts a sourness to a composition. Other souring agents include malic acid, acetic acid, tartaric acid, gluconodeltalactone, phosphoric acid, succinic acid, phytic acid, lactic acid or salts thereof. The souring agent (for example citric acid) may be provided in an encapsulated form. The encapsulation provides a coating that isolates the souring agent from other components and from air and moisture prior to its use. Several encapsulated forms of citric acid, or other souring agents, are commercially available. For example, the encapsulation may be with a water-soluble coating.

[0035] The amount of sweetener required depends on the nature and strength of the sweetener being considered. Typically, it is 0.10 to 4 g per litre. For example, the sweetener may be aspartame at 0.5 to 4g per litre, for example 2.5 to 4.0 g per litre, for example 3.0g per litre, for example 3.86g per litre. Those quantities of aspartame are particularly suitable when used with orange flavouring, for example orange flavouring at 0.2 to 1.8g per litre, for example 1.0 to 1.8g per litre, for example 0.3g per litre, 0.875g per litre or 1.2g per litre. For example, the sweetener may be aspartame at 1.0 to 2.5g per litre, for example 1.5 to 2.0g per litre, for example 1.75g per litre.

[0036] Thus there is provided a kit comprising a second colon cleansing solution comprising:

a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of

1. (i) ascorbic acid and
2. (ii) one or more salts of ascorbic acid

the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0;

b) 10 to 200 g per litre PEG.

c) one or more electrolytes;

e) optionally one or more flavouring agents; and

f) optionally one or more sweeteners.

[0037] It will be apparent to the reader of this specification, that the term "comprising" and grammatical variations thereof, in relation to embodiments of the invention described, may be substituted in all cases (unless the context dictates otherwise) with the term "consisting essentially of' or "consisting of'. In the case of a solution that "consists of' or "consists essentially of' the stated components, the balance is in each case made up of water.

[0038] In particular, there is provided a kit comprising a second colon cleansing solution comprising:

a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of

1. (i) ascorbic acid and
2. (ii) one or more salts of ascorbic acid

the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0;

b) 10 to 200 g per litre PEG having an average molecular weight of 3000 to 4000 Da;

c) sodium chloride and potassium chloride;

e) optionally one or more flavouring agents; and

f) optionally one or more sweeteners.

[0039] Each of c) and d) may be present in the concentrations described above. Each of e) and f) may be as described above and/or be in the concentrations described above.

[0040] In particular, there is provided a kit comprising a second colon cleansing solution comprising:

a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of

1. (i) ascorbic acid and
2. (ii) one or more salts of ascorbic acid

the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0;

b) 10 to 200 g per litre PEG having an average molecular weight of 3000 to 4000 Da;

c) sodium chloride and potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0041] In one embodiment, one or more components of c), d) (when present), e) and f) are present in the solution. In an alternative presentation, some or all of components c), e) and f) may be provided separately from the solution, for example in a tablet or capsule. For example, components c) and d) may be provided in tablet form. In an embodiment, the solution may comprise a) the ascorbate component and b) PEG, and optional flavouring and sweetener (e) and f)), and a tablet or capsule may comprise c) the one or more electrolytes, again with

optional flavouring and sweetener (e) and f). The flavouring and sweeteners need not be the same in the tablet or capsule as in the solution.

[0042] In one embodiment, there is provided a kit comprising a second colon cleansing solution comprising:

a)

1. (i) 12 to 20g per litre ascorbic acid and
2. (ii) 80 to 120g per litre sodium ascorbate

the components (i) and (ii) being present in a weight ratio of from 1:5063 to 1:7.875;

b) 60 to 100g per litre PEG having an average molecular weight of 3000 to 4000 Da;

c) 3 to 8g per litre sodium chloride and 1 to 7g per litre potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0043] In an embodiment, the solution consists essentially of those components; that is to say that it does not contain any further components in significant quantities. The solution may, for example, not contain any sulphate.

[0044] For example, there is provided a kit comprising a second colon cleansing solution consisting essentially of:

a)

1. (i) 14 to 16g per litre ascorbic acid and
2. (ii) 92 to 100g per litre sodium ascorbate

b) 75 to 85 per litre PEG having an average molecular weight of 3000 to 4000 Da;

c) 6.0 to 6.8g per litre sodium chloride and 2.0 to 2.8g per litre potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0045] For example, there is provided a kit comprising a second colon cleansing solution consisting essentially of:

a)

1. (i) 15.08g per litre ascorbic acid and
2. (ii) 96.22g per litre sodium ascorbate

b) 80g per litre PEG having an average molecular weight of 3000 to 4000 Da;

c) 6.4g per litre sodium chloride and 2.4g per litre potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0046] For example, the flavouring and sweetener may be 1.20g per litre orange flavour and 3.86g per litre aspartame. For example, the flavouring and sweetener may be 3.20g per litre citrus flavour and 1.75g per litre aspartame. For example, the flavouring and sweetener may be 4.20g per litre orange grapefruit flavour and 1.75g per litre aspartame.

[0047] Preferably, the second colon cleansing solution is hyper-osmotic. That is to say that it has a higher osmotic strength than blood in the human body. It may, for example have a measured osmolality in the range 500 to 2000 mOsmol/kg. For example, the osmolality may be in the range 700 to 1800 mOsmol/kg. For example, the solutes in 500ml of the solution may have a measured V(350) value of from 1000 to 2000ml, for example from 1300 to 2000ml, for example from 1400 to 1900ml, and be in a volume of 400 to 600ml, for example 500ml. The V(350) value is the volume of water that is required to provide a solution with an osmolality of 350mOsmol/kg, the total volume being the final volume after a volume water has been added to a solution having an initial volume.

[0048] Osmolality can be measured in various ways. In general, either freezing point depression or vapour-pressure alteration is used. For example, an Advanced Instruments, Inc Model 3250 osmometer (a freezing point depression device) can be used. Vapour pressure measurement can also be used, for example using an ELITech Group Vapro 5600 device. Osmolality values cited herein are preferably taken to be values measured using a freezing point depression osmometer, for example using an Advanced Instruments, Inc Model 3250 osmometer following standard operating procedure.

[0049] Also provided is a kit comprising a colon cleansing solution comprising:

1. a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of
    1. (i) ascorbic acid and
    2. (ii) one or more salts of ascorbic acid

   the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0; and
2. b) 10 to 200 g per litre PEG having an average molecular weight of 3000 to 4000 Da; and 500ml of the solution having a V(350) osmolality value of from 1300 to 2300ml.

[0050] For example, 500ml of the solution may have a V(350) osmolality value of from 1500 to 2100ml, for example from 1700 to 2000ml, for example from 1800 to 1900ml.

b) Additional optional contents of solutions

[0051] Unless it is stated otherwise, the solutions may include one or more additional optional components:

(i) antioxidants

[0052] In general it is not necessary for the solutions to include preservatives or anti-oxidants. Nevertheless, low levels of anti-oxidants or preservatives may be used if required.

(ii) laxatives

[0053] In general, the solutions described herein are effective without the need for any additional active ingredients. Nevertheless, a further active ingredient may be included if required. For example, a laxative may be present, for example a stimulant laxative. For example, bisacodyl, castor oil, senna or bisoxatin may be used. An example of a colon cleansing solution containing bisoxatin is known from WO2013001315.

(iii) Contrast media

[0054] For certain uses, one or more contrast media can be included in a solution of the invention. Examples of contrast media include barium or iodine products, diatrizoate (marketed, for example, as HYPAQUE 50), metrizoate (marketed, for example, as ISOPAQUE 370), ioxalgate (marketed, for example, as HEXABRIX), iopamidol (marketed, for example, as ISOVUE 370), iohexol (marketed, for example, as OMNIPAQUE 350), ioxilan (marketed, for example, as OXILAN 350), iopramide (marketed, for example, as ULTRA VIST 370), iodixanol (marketed, for example, as VISIPAQUE 320) and/or a diatrizoic acid or its anionic form diatrizoate (also known as amidotrizoic acid, or 3,5-diacetamido-2,4,6-triiodobenzoic acid; marketed, for example, as HYPAQUE). Alternatively, the solution of the invention may be used in conjunction with (e.g., simultaneously, before or after) administration of a contrast agent or contrast media.

(iv) Dyes and stains.

[0055] For certain uses (eg fluorescence endoscopy), one or more dyes or stains that are markers of particular mucosal pathology can be included in a solution of the invention. Stains may be selective . For example, hexaminolevulinate may be used, for example as its HCl salt (marketed as CYSVIEW). Other markers of colonic or rectal mucosal pathology can be used. For example methylene blue, which can stain the normal mucosa yet polyps do not stain and become more clearly visible.

[0056] Further dyes and stains that may be mentioned include: Curcumin, Riboflavin, Riboflavin-5'-phosphate, Tartrazine, Quinoline Yellow, Sunset Yellow, FCF Orange, Yellow S, Cochineal, Carminic acid, Carmines, Azorubine, Carmoisine, Ponceau 4R, Cochineal Red A, Allura Red AC, Patent Blu EV, Indigotine, Indigo carmine, Brilliant Blue FCF, Chlorophylls and chlorophyllins, Copper complexes of chlorophylls and chlorophyllins, Green S, Plain caramel, Brilliant Black BN, Black PN, Vegetable carbon, Brown HT, Carotenes, Lutein, Beetroot Red, betanin, Anthocyanins, Calcium carbonate, Titanium dioxide, Iron oxides and hydroxides, Amaranth, Brown F , Erythrosine, Lithol Rubine B and/or Red 2G. Further dyes and stains that may be mentioned include: acid fuchsine, Alba red, Alizarin cyanine green F, Alizurol purple S5, Allura Red AC, Alphazurine FGBrilliant lake red R, Dibromofluorescein, Diiodofluorescein, Eosine, Erythrosine yellowish Na, Fast green FCF, Flaming red, Fluorescein, Helindone pink CN, Indanthrene blue, Lake bordeaux B, Lithol rubin B Ca, Naphthol yellow 5, Orange II, Phloxine B, Ponceau 5X, Pyranine concentrated, Quinizarinegreen 5S, Tetrabromo-fluorescein, Tetrachlorotetrabromo fluorescein, Toney red, Uranine, Alcian Blue, Anazolene Sodium, Brilliant Green, Cantaxanthin, Carthamin, Citrus Red 2, Evan's Blue, Fast Green FCF, Indocyanine Green, Methyl Blue, Methylene Blue, N-(p-Methoxyphenyl)-p- phenylenediamine, Ponceau 3R, Ponceau SX, Pyranine, Rhodamine B, Saunders Red, Sudan Black B, Sulphan Blue, Tolonium Chloride, and/or Vital Red or equivalents or any combination thereof.

[0057] Alternatively, the solution of the invention may be used in conjunction with (e.g., simultaneously, before or after) administration of a dye or stain. A dye or a stain may be provided in slow or delayed release form, for example delayed release methylene blue (for example MMX format of colonic-released methylene blue) may be mentioned.

(v) Surfactants

[0058] A surfactant may be included in a solution of the invention. A surfactant may assist in avoiding the persistence of bubbles in the colon. Such bubbles can interfere with the visualisation of features of the colon during colonoscopy. Surfactants that may be mentioned include simethicone (or any mixture of polydimethylsiloxane and silica gel), dimethicone. Bowel cleansing solutions containing simethicone are described in WO2009052256.

(vi) Lubricants

[0059] A lubricant may be included in a solution of the invention. The inclusion of a lubricant can help with a colonoscope insertion and facilitation within the performance of the colonoscopy. Suitable lubricants include glycerol or silicone.

(vii) Biofilm-disrupting compounds

[0060] A biofilm disrupting compound may be included in a solution of the invention. A compound that disrupts biofilms may assist in separating an adherent polysaccharide DNA - containing layer, the so-called "biofilm" from the colonic mucosa. Removal of that layer may assist in achieving a cleaner and/or more easily visualized or stained mucosa.

[0061] Biofilm-disrupting components or agents that may be mentioned include enzymes such as deoxyribonuclease (DNase), N-acetylcysteine, alginate lyase, glycoside hydrolase dispersin B; Quorum-sensing inhibitors e.g., ribonucleic acid III inhibiting peptide, Salvadora persica extracts, Competence-stimulating peptide, Patulin and penicillic acid; peptides - cathelicidin-derived peptides, small lytic peptide, PTP-7 (a small lytic peptide, see e.g., haridia (201 1) J. Microbiol. 49(4):663-8, Epub 201 1 Sep 2), Nitric oxide, neo- emulsions; ozone, lytic bacteriophages, lactoferrin, xylitol hydrogel, synthetic iron chelators, cranberry components, curcumin, silver nanoparticles, Acetyl- 1 1 - keto-P-boswellic acid (AKBA), barley coffee components, probiotics, sinefungin, S-adenosylmethionine, S- adenosyl-homocysteine, Delisea furanones, N-sulfonyl homoserine lactones and/or macrolide antibiotics or any combination thereof.

[0062] Alternatively, the solution of the invention may be used in conjunction with (e.g., simultaneously, before or after) administration of a biofilm-disrupting compound. A biofilm-disrupting compound may be administered towards the end of ingestion of the solution of the invention, or shortly after completion of ingestion of the solution of the invention, so as to disrupt the biofilm most just before the colonoscopy.

(viii) Organic acids

[0063] Some of the osmotic load of the solution may be provided by an organic acid or salts of an organic acid other than ascorbic acid. For example, citric acid and/or salts thereof may replace some or all of the ascorbate in solutions. Throughout this description, ascorbic acid may be replaced with citric acid. A salt of ascorbate may be replaced with the salt of citrate. Sodium citrate, potassium citrate and magnesium citrate are particularly preferred.

c) Uses of solutions of the invention

[0064] The solutions of the invention find use in cleansing the colon or bowel. They are also

useful in the treatment of faecal impaction or constipation.

[0065] When carrying out a bowel cleansing treatment, a subject typically takes a single dose or a split dose of cleansing solution. In a split-dose treatment, typically two doses are taken separated by a time interval, for example an overnight interval. Alternatively, in a split-dose treatment two doses may be taken on the same day, for example during the day before a therapeutic or surgical procedure, or during the day of a therapeutic or surgical procedure. Each dose in a split dose treatment is smaller than the dose in the single dose treatment. In a split dose treatment, the two doses may each have the same composition, or they may be different.

[0066] For a single dose treatment, the solution of the invention may be ingested in a volume of 700 to 1500ml. For example, the subject may ingest from 750ml to 1300ml of the solution, for example 800 to 1200ml, for example 900 to 1100 ml, for example 1000ml. For example 33 or 34 US fluid ounces may be ingested. In an embodiment, the subject may ingest some additional clear fluid. The additional clear fluid may be ingested after ingesting the solution. Alternatively, the additional clear fluid may be co-administered with the intake of the solution of the invention. By "co-administered" is meant the coordinated ingestion of a solution of the invention with clear fluid; that is to say that the subject ingests some of the solution of the invention but not necessarily the whole dose, then some clear fluid and then more solution of the invention.

[0067] For a split dose treatment, the solution of the invention may be taken as one or both of the doses, each dose having a volume of 200 to 1000ml. For example, the subject may ingest (as one of the doses) 300ml to 1000ml of the solution, for example 300ml to 900ml, for example 300ml to 800ml, for example 400ml to 700ml, for example 400 to 600ml, for example 450 to 550 ml, for example 500ml. For example 16 or 17 US fluid ounces may be ingested.

[0068] The combined volume of the first and second doses is preferably less than 2 litres. Preferably, it is 1750ml or less, for example 1500ml or less, for example 1250ml or less. For most adult subjects, a combined volume of more than 500ml is used, for example more than 750ml. For example, a combined volume of from 500ml to 1750ml is used, for example from 750ml to 1500ml, for example from 1000ml to 1500ml, for example 1000ml or 1250ml. For example the first dose may have a volume of 500ml (for example a volume of 16 or 17 US fluid ounces) or 750ml (for example a volume of 25 or 26 US fluid ounces) and the second dose may have a volume of 500ml (for example a volume of 16 or 17 US fluid ounces).

[0069] In an embodiment, the subject may ingest some additional clear fluid with each or either dose of colon cleansing solution. The additional clear fluid may be taken after ingesting a dose of the solution. Alternatively, the additional clear fluid may be co-administered with the intake of a dose of the solution of the invention; that is to say that the subject ingests some of the solution of the invention but not necessarily the whole dose, then some clear fluid and then more solution of the invention.

[0070] In the method, there is typically a time interval between ingesting the first dose and ingesting the second dose. Generally, the time interval is at least 4 hours, for example 6 hours or more, for example 8 hours or more. Typically, the time interval is less than 15 hours. The time interval between starting to take the first dose and starting to take the second dose may be, for example, the time between an evening and the following morning, for example 12 to 16 hours, for example 14 hours. For example, the subject may sleep (for example overnight) between taking the first and second doses.

[0071] Alternatively, the time interval between ingesting the first dose and ingesting the second dose can be at least 10 minutes, for example from 10 minutes to 4 hours, for example from 30 minutes to 4 hours, for example from 30 minutes to two hours. For example, the subject may ingest the first and second colon doses the evening before a surgical or diagnostic procedure. The time interval between ingesting the first solution and ingesting the second solution can be determined by the time it takes for the subject to experience a bowel movement. For example the subject takes the second dose when the first bowel movement has occurred after completing ingestion of the first solution. Alternatively, the subject ingests the second dose when the first bowel movement has occurred even if ingestion of the first dose is not complete.

[0072] During the ingestion of the first or second dose, or during the time interval between the ingestion of the first dose and the second dose, the subject may additionally take a stimulant laxative (also known as a prokinetic agent). A stimulant laxative can assist in bringing about good cleansing. Examples of stimulant laxatives include contact laxatives, for example bisacodyl, castor oil, senna or bisoxatin. Examples of stimulant laxatives also include additional osmotic agents for example magnesium salts, for example magnesium citrate. If a stimulant laxative is included in the regimen, the length of the time interval can be shortened. For example, it may be 10 minutes to 15 hours, for example 1 to 15 hours, for example 1 to 12 hours, for example 2 to 10 hours.

[0073] During the time interval between the administration of the first dose and the second dose, it is very likely that the subject will experience a bowel movement. Advantageously, the subject waits until the bowel movement has occurred before taking the second dose.

[0074] In a split dose treatment, the solution of the invention may be taken for one or for both of the doses. Preferably, the solution of the invention is taken as the second solution. For example, the subject may ingest 300ml to 1000ml of the solution of the invention as the second solution, for example 300ml to 900ml, for example 300ml to 800ml, for example 400ml to 700ml, for example 400 to 600ml, for example 450 to 550 ml, for example 500ml. For example 16 or 17 US fluid ounces may be ingested.

[0075] The first solution may be a solution of different constitution from the second solution. Thus, in a preferred embodiment of a split dose bowel cleansing treatment, a subject takes a dose of an initial cleansing solution, optionally followed by some additional clear fluid. After an interval, the subject then takes a dose of the solution of the invention, optionally followed by some additional clear fluid.

[0076] The volume of clear fluid that a subject ingests after the first or second dose may be in a range with a lower limit of 100ml, 200ml, 300ml, 400ml or 500ml. Preferably, the lower limit is 300ml, 400ml or 500ml. The volume may be in a range with an upper limit of 1200ml, 1100ml, 1000ml, 900ml or 800ml. For example the volume may be in the range 100ml to 1200ml, for example 200ml to 1100ml, for example 300ml to 1000ml, for example 500ml to 900ml, for example 1000ml, for example 875ml, for example 500ml to 800ml. For example the volume may be in the range 300 ml to 900 ml, for example 400 ml to 800 ml, for example 500 ml to 800 ml. The additional clear fluid may be ingested in a volume of at least 500 ml. For example it may be at least 16 or 17 US fluid ounces. The instructions provided to the subject may suggest that the additional clear fluid is ingested over a period of approximately one hour, for example in 150 to 200ml fractions every 15 to 20 minutes. The additional clear fluid may be taken after taking a dose of the solution. Alternatively, the additional clear fluid may be co-administered with the intake of a dose of the solution of the invention; for example, the subject may ingest clear fluid between fractions of the solution of the invention; for example the subject may ingest a cup of the solution of the invention, followed by a cup of clear fluid, followed by further cups of the solution of the invention.

[0077] A clear fluid for taking as the additional clear fluid, or for use as the clear fluid when making up a solution, may be any fluid that allows inspection of colonic output. The clear fluid should also not impede inspection of the colon during the colonoscopy. Typically the clear fluid is a water-based beverage, including, for example, water, lemonade, cola drinks, cordial drinks, clear fruit juices and even clear alcohol-containing beverages, for example beer. It is desirable that the clear fluid does not contain substantial amounts of or essentially any dietary fibre, as such fibre interferes with the cleansing of the colon according to the present invention. Accordingly, fruit juices, for example orange juice and kiwi juice, and fruit "squashes" should be strained before use. Clear fruit cordials, for example lime cordial or tea (for example green tea), are generally suitable. In view of the desirability of avoiding drinks containing glucose, so as to reduce the risk of explosive concentrations of hydrogen or methane building up in the gut, "diet" drinks containing no or low sugar are especially suitable, for example liquid drinks for diabetics, diet Coke (RTM), diet lemonade, dietary carbonated drinks or dietary cordials. The most preferred clear fluid is water.

[0078] The method of the invention may be used to cleanse the colon prior to carrying out a diagnostic, therapeutic or surgical procedure on the colon, rectum or anus or elsewhere in the abdomen in a subject. The subject is most preferably a human. The diagnostic or surgical procedure may, for example, be colonoscopy (such as cap-assisted colonoscopy and/or narrow-band colonoscopy), barium enema examination, sigmoidoscopy (for example flexible sigmoidoscopy) or colon surgery. The method of the invention may be a method of cleansing the colon prior to a surgical or diagnostic procedure comprising administering the first solution and then after a time interval administering the second solution prior to said procedure.

[0079] The solutions, compositions and kits described herein also find use in the treatment of constipation and faecal impaction. They also find use in the treatment of severe bacterial

infections of the bowel. The invention thus provides solutions, compositions and kits as described herein for use in the treatment of constipation or faecal impaction, or in the treatment of severe bacterial infections of the bowel. The invention also provides methods of treating constipation or faecal impaction, or in the treating severe bacterial infections of the bowel comprising administration of solutions as described herein.

[0080] As mentioned above, a bowel cleansing treatment typically involves a subject taking a single dose or a split dose of cleansing solution. The volume of solution that a subject takes in a single dose treatment is described hereinabove. The subject may take some additional clear fluid after taking the solution as described hereinabove. The volume of solution that a subject takes in a split dose treatment is described hereinabove. The subject may take some additional clear fluid after each or either dose the solution as described hereinabove.

d) Compositions for preparing doses of solutions

[0081] Also provided is a kit comprising a composition (for example a dry composition, for example a powder) for the preparation of a second colon cleansing solution. A composition can be in a quantity for the preparation of a dose of the solution, for example a 500ml dose (for example a 16 or 17 US fluid ounce dose). Also provided is a kit comprising a composition for admixture with water, wherein the composition is optionally presented in two or more parts and comprises:

1. a) 150 to 400 mmol ascorbate anion provided by a mixture of:
    1. (i) ascorbic acid and
    2. (ii) one or more salts of ascorbic acid

   the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0; and
2. b) 5 to 100 g polyethylene glycol.

[0082] For example, the components may be in dry powder, granular or other dry form. They may alternatively be in the form of concentrates or slurries. Components may be in the same or different physical forms. For example, the composition is a dry composition, for example a dry powder composition. For example, one or both of components a) and b) are dry powders. In a dry powder, it is possible for one or more components to be a salt hydrate.

[0083] As set out above in section 3a), the ascorbate anion is provided by a mixture of ascorbic acid and one or more salts of ascorbic acid. Preferred forms of the ascorbate component are as set out above in relation to solutions.

[0084] The composition preferably comprises ascorbate anion in an amount of 150 to 350mmol, for example 175-325mmol, for example 225-300 mmol.

[0085] Ascorbic acid has a molecular weight of 176g/mol and sodium ascorbate has a molecular weight of 198g/mol. Accordingly, the 150 to 400 mmol ascorbate anion can be provided by 3.3 to 12.8g ascorbic acid and 24.3 to 69g sodium ascorbate, for example 5.0 to 10g ascorbic acid and 40 to 60g sodium ascorbate; for example 6.0 to 10g ascorbic acid and 40 to 60g sodium ascorbate; for example 7.0 to 8.0g ascorbic acid and 44 to 52g sodium ascorbate; for example 7.0 to 8.0g ascorbic acid and 46 to 50g sodium ascorbate.

[0086] Potassium ascorbate has a molecular weight of 214g/mol. Accordingly, the 150 to 400 mmol ascorbate anion can be provided by 3.3 to 12.8g ascorbic acid and 26 to 75g potassium ascorbate, for example 5.0 to 10g ascorbic acid and 45 to 65g potassium ascorbate; for example 7.0 to 8.0g ascorbic acid and 47 to 56g sodium ascorbate.

[0087] Magnesium ascorbate has a molecular weight of 374.5g/mol and each mole of magnesium ascorbate provides two moles of ascorbate. Accordingly, the 150 to 400 mmol ascorbate anion can be provided by 3.3 to 12.8g ascorbic acid and 23 to 65g magnesium ascorbate, for example 5.0 to 10g ascorbic acid and 38 to 57g magnesium ascorbate; for example 7.0 to 8.0g ascorbic acid and 42 to 49g magnesium ascorbate.

[0088] In solid form, ascorbic acid is typically made up of protonated free ascorbic acid. In calculations of concentrations of "ascorbate anion" herein, the number of moles of "ascorbate anion" is taken as the total concentration of all ascorbate anion present, including the proportion that is protonated.

[0089] The weight of the ascorbate component may be 20 to 85g, for example 25 to 75g, for example 20 to 60g, for example 50 to 60g.

[0090] In an embodiment, the ascorbate component comprises (or consists essentially of) sodium ascorbate and ascorbic acid. For example, they may be present in a total amount and in a weight ratio as mentioned immediately above.

[0091] Preferred forms of the PEG are as set out above in section 3a), in relation to solutions of the invention. The composition comprises 5 to 100 g of PEG. Preferably, the composition comprises 10 to 80g of PEG, more preferably 20 to 60g, for example 30 to 50g, for example 37.5 to 42.5g, for example 40 g of PEG.

[0092] The composition may additionally comprise one or more of:

c) one or more electrolytes;

d) one or more alkali metal or alkaline earth metal sulphates;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0093] Preferred electrolytes are as set out above in section 3a), in relation to solutions. For example, the composition may comprise sodium chloride in an amount of 0.5 to 5g, for example 1.5 to 4 g, for example 2.0 to 3.5g, for example 2.8g or 3.2g. For example, the composition may comprise potassium chloride in an amount of 0.5 to 5g, for example 0.5 to 3.5 g, for example 0.75 to 2.5g, for example 0.75 to 1.5g,for example 1.0 to 1.4g, for example 1.2g or 1.3g. In an embodiment, the composition is essentially free from sodium bicarbonate, for example essentially free from any bicarbonate.

[0094] Preferred alkali metal or alkaline earth metal sulphates are as set out above in section 3a), in relation to solutions. For example, the composition may comprise a sulphate component in an amount of 1 to 10g, for example 2.5 to 7.5g, for example 4 to 7.5g, for example 5 to 7g, for example 6g. The one or more sulphate salts may be provided in any pharmaceutically acceptable form: they may each be anhydrous, or be in a hydrated form. The weights mentioned herein refer to the weight of the sulphate salt excluding any water of hydration. A hydrate form may be present in the dry powder composition, and that composition is still considered "dry" herein. In an alternative preferred embodiment, the composition does not comprise a sulphate component; that is to say that the composition is essentially free from alkali metal sulphates and alkaline earth metal sulphates; in particular essentially free from sodium sulphate, potassium sulphate and magnesium sulphate.

[0095] Preferred flavouring agents are as set out above in section 3a), in relation to solutions . For example the amount of flavouring agent may be 0.025 to 2.25g, for example 0.025 to 1.0 g, for example 0.1 to 0.9g, for example 0.5 to 0.9g, for example 1.5 to 2.25g, for example 0.15g or 0.6g, for example 1.6 or 2.1g.

[0096] Preferred sweeteners are as set out above in section 3a), in relation to solutions. The amount of sweetener required depends on the nature and strength of the sweetener being considered. For example the amount of sweetener may be 0.05 to 2 g, for example 0.25 to 2g, for example 1.25 to 2g, for example 1.5g, for example 1.93g. Those quantities of aspartame are particularly suitable when used with orange flavouring, for example orange flavouring at 0.1 to 0.9g, for example 0.5 to 0.9g, for example 0.15g, 0.4375g or 0.6g. For example, the sweetener may be aspartame at 0.5 to 1.25g, for example 0.75 to 1.0g, for example 0.875g.

[0097] In particular, there is provided a kit comprising a composition comprising :

a) 150 to 400 mmol ascorbate anion provided by a mixture of:

1. (i) ascorbic acid and
2. (ii) one or more salts of ascorbic acid

the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0;

b) 5 to 100 g PEG having an average molecular weight of 3000 to 4000 Da.

c) sodium chloride and potassium chloride;

e) optionally one or more flavouring agents;

f) optionally one or more sweeteners.

[0098] Each of c) and d) may be present in the amounts described above. Each of e) and f) may be as described above and/or be in the amounts described above.

[0099] In one embodiment, there is provided a kit comprising a composition comprising:

a)

1. (i) 6.0 to 10g ascorbic acid and
2. (ii) 40 to 60g sodium ascorbate

the components (i) and (ii) being present in a weight ratio of from 1:5063 to 1:7.875;

b) 30 to 50g PEG having an average molecular weight of 3000 to 4000 Da;

c) 1.5 to 4g sodium chloride and 0.5 to 3.5g potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0100] In one embodiment, there is provided a kit comprising a composition comprising:

a)

1. (i) 7.43g ascorbic acid and
2. (ii) 48.11g sodium ascorbate

b) 40g PEG having an average molecular weight of 3000 to 4000 Da;

c) 3.20g sodium chloride and 1.20g potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0101] For example, the flavouring and sweetener may be 0.60g orange flavour and 1.93g aspartame. For example, the flavouring and sweetener may be 1.60g citrus flavour and 0.875g aspartame. For example, the flavouring and sweetener may be 2.10g orange grapefruit flavour and 0.875g aspartame.

[0102] In an embodiment, the composition consists essentially of those components; that is to say that it does not contain any further components in significant quantities. The composition may, for example, not contain any sulphate.

[0103] One or more of components a) to f) may be presented in solid form, or in semi-solid form (for example in gel form).

[0104] In one embodiment, the one or more components of c), d) (when present), e) and f) are present in the composition for making up a solution. In an alternative presentation, some or all of components c), d) (when present), e) and f) may be provided separately from the composition for making up the solution, for example in a tablet or capsule. In an embodiment, there may be provided the ascorbate component and PEG, and optional flavouring and sweetener, in a form for admixture with water, and a tablet or capsule comprising the one or more electrolytes and/or the one or more alkali metal or alkaline earth metal sulphates, again with optional flavouring and sweetener. The flavouring and sweeteners need not be the same in the tablet or capsule as in the composition for admixture with water.

[0105] In some embodiments, it is desirable to package the ascorbate and the PEG components separately from each other.

[0106] In an embodiment, the composition can be provided to the subject with a plurality of flavouring agents (each optionally with one or more sweeteners), each separately packaged. The subject can then select a preferred flavouring (or flavouring and sweetener combination) according to his or her taste. The subject also has the choice of not using any flavouring or sweetener at all.

[0107] It will be apparent to the reader that all compounds and compositions described herein are of a nature and quality suitable for mammalian (especially human) consumption. For example, they are of pharmaceutical grade. The pharmaceutically acceptable compositions described herein may be provided in packaged form with instructions for use.

f) Methods of preparing solutions and compositions

[0108] The invention further provides a method of preparing a solution of the invention comprising combining the components of the solution with water. The method comprises the step of combining the components with water and admixing. Some or all of the components may be in physical association with each other before the water is added. In some embodiments, the components of the composition are provided in more than one part; that is to say that they are packaged separately. All of the components may be combined with each other before combining with water. For example, if flavouring agent and sweetener are packaged separately from other components, they may be combined with the other components before combining with water. One or some of the components may be combined

with water and admixed in a first step and then some or all of the remaining components may be added in a second step. For example, the components may be in dry form, for example in powder form.

[0109] As set out above in section 3d), the invention provides a composition (for example a dry composition, for example a powder) for the preparation of a solution of the invention. The invention further provides a method of preparing a composition of the invention comprising combining the components of the composition. For example, the method may be a method of preparing a composition of the invention in powder form. As set out in section 3d) above, the components for the preparation of a solution of the invention may be presented in two or more parts. The invention thus further provides a method of preparing a component of a kit of the invention comprising combining some, but not all of the components of the composition. Thus there is disclosed a method comprising blending a mixture of:

1. (i) ascorbic acid: 1 part and
2. (ii) one or more salts of ascorbic acid: 5.063 to 7.875parts

[0110] The salt of ascorbic acid can be sodium ascorbate. A mixture of ascorbic acid and sodium ascorbate in a molar ratio of from 1:4.5 to 1:7.0 has ascorbic acid and sodium ascorbate present in a weight ratio of 1:5.063 to 1:7.875. A more preferred ratio is 1:5.344 to 1:7.594; more preferably from 1:5.625 to 1:6.75; for example from 1:6.075 to 1:6.525, for example 1:6.38.

[0111] The method may comprise blending a mixture of:

1. (i) ascorbic acid and
2. (ii) one or more salts of ascorbic acid

the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0.

[0112] Preferred salts of ascorbic acid are as set out above in section 3a). Preferred ratios of components (i) and (ii) are as set out above in section 3a).

[0113] The method may further comprise blending a mixture of:

1. a) ascorbate anion: 0.82 to 4.0 parts;
2. b) polyethylene glycol: 1.0 part;

c1) sodium chloride: 0.005 to 1.0 parts; and

c2) potassium chloride: 0.005 to 1.0 parts;

the ascorbate anion being provided by

1. (i) ascorbic acid and

2. (ii) one or more salts of ascorbic acid

the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0.

[0114] The components may be weighed out and added together before blending, or the components may be added into a blend mixture in any desired order.

[0115] Blending of the compositions in bulk may, for example, be carried out on a 100Kg, 500Kg or 1000Kg scale. After blending, the composition is divided into smaller portions for packaging into dosage amounts. Thus there is disclosed a method comprising the step of dividing bulk composition as set out in section 3e) above into smaller portions. Also disclosed is a method comprising the step of filling containers with individual dosage amounts of bulk composition as set out in section 3e). Thus there is disclosed a method comprising the step of filling a container with a composition as set out in section 3d). The composition as set out in section 3d) may be presented in two or more parts. The method may thus comprise the step of filling a container with some but not all of the components of a composition as set out in section 3d).

6. Methods of cleansing and solutions for use in them

a) Split-dose colon cleansing treatments

[0116] The solutions and compositions of the first and second aspects set out in sections 2 and 3 above find particular use in split dose colon cleansing treatments in which the subject takes two different agents (for example two different solutions): a first colon cleansing agent (for example solution), followed by a second colon cleansing agent (for example solution). Herein, the "second colon cleansing agent" means the agent that is taken chronologically second, after the "first colon cleansing agent". Preferably, the solution of the first or second aspect is the second colon cleansing agent. Alternatively, it may be the first agent. Thus there is disclosed, in a third aspect a method of cleansing the colon of a mammal comprising:

- the subject taking an effective amount of a first colon cleansing agent; and then
- the subject taking an effective amount of a second colon cleansing agent,

the second colon cleansing agent being a solution of the first or second aspect described above. Preferably, the first colon cleansing agent is of different composition from the second colon cleansing agent. The first colon cleansing agent may be a colon cleansing solution. Alternatively, it may be a colon cleansing agent in solid form, for example in the form of a tablet, for example a PEG-containing tablet, or a bisacodyl-containing tablet. The first colon cleansing agent may, for example, contain a laxative, for example a stimulant laxative. For example, bisacodyl, castor oil, senna or bisoxatin may be used.

[0117] Also disclosed is a method of cleansing the colon of a mammal comprising:

- the subject taking an effective amount of a first colon cleansing agent; and then
- the subject taking an effective amount of a second colon cleansing agent,

the second colon cleansing agent being a solution comprising

1. a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of:
    1. (i) ascorbic acid and
    2. (ii) one or more salts of ascorbic acid

   the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0; and
2. b) optionally 10 to 200 g per litre polyethylene glycol.

[0118] Also disclosed is a method of cleansing the colon of a mammal comprising:

- the subject taking an effective amount of a first colon cleansing agent; and then
- the subject taking an effective amount of a second colon cleansing agent,

the second colon cleansing agent being a solution comprising

1. a) 360 to 440 mmol per litre ascorbate anion provided by one or more salts of ascorbic acid; and
2. b) optionally 10 to 200 g per litre polyethylene glycol;

the solution being essentially free from ascorbic acid.

[0119] The method may be used to cleanse the colon prior to carrying out a diagnostic, therapeutic or surgical procedure on the colon, rectum or anus or elsewhere in the abdomen. The diagnostic or surgical procedure may, for example, be colonoscopy, barium enema examination, sigmoidoscopy or colon surgery. The method is generally finished less than 8 hours before carrying out the diagnostic, therapeutic or surgical procedure on the colon, rectum or anus or elsewhere in the abdomen. Preferably, it is finished less than 4 hours before.

[0120] Also disclosed is a method of conducting a diagnostic or surgical procedure, for example, a colonoscopy, barium enema examination, sigmoidoscopy or colon surgery, comprising the steps of:

1. a) cleansing the colon by a method herein described and then
2. b) carrying out the diagnostic or surgical procedure.

[0121] Also disclosed is a first colon cleansing agent, and a second colon cleansing agent, for use in a method of cleansing the colon comprising:

- the subject taking an effective amount of a first colon cleansing agent;

- the subject taking an effective amount of a second colon cleansing agent,

the second colon cleansing agent being a solution of the first or second aspect described above.

[0122] Also disclosed is a first colon cleansing agent, and a second colon cleansing agent, for use in a method of cleansing the colon comprising:

- the subject taking an effective amount of a first colon cleansing agent;
- the subject taking an effective amount of a second colon cleansing agent,

the second colon cleansing agent being a solution in water of:

1. a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of
    1. (i) ascorbic acid and
    2. (ii) one or more salts of ascorbic acid

   the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0; and
2. b) optionally 10 to 200 g per litre polyethylene glycol.

[0123] In an embodiment, the first agent is different from the second.

[0124] Also disclosed is a first colon cleansing agent, and a second colon cleansing agent, for use in a method of cleansing the colon comprising:

- the subject taking an effective amount of a first colon cleansing agent;
- the subject taking an effective amount of a second colon cleansing agent,

the second colon cleansing agent being a solution in water of:

1. a) 360 to 440 mmol per litre ascorbate anion provided by one or more salts of ascorbic acid; and
2. b) optionally 10 to 200 g per litre polyethylene glycol.

the solution being essentially free from ascorbic acid.

[0125] In an embodiment, the first agent is different from the second. Further details of possible first colon cleansing agents are provided below in section 6b)

[0126] The second colon cleansing agent is preferably as described hereinabove in sections 2 and 3 in relation to solutions and uses of the first and second aspects. It is preferably used in a volume as described hereinabove in relation to solutions and uses as described hereinabove in sections 2 and 3.

[0127] The first and second colon cleansing agents may be provided in a kit. Further details of such kits are provided in section 8) below.

b) The "first" colon cleansing agent

[0128] The first cleansing agent may be a solution, referred to as the first colon cleansing solution. The first colon cleansing solution may, for example, be a bowel content suspending agent. The first colon cleansing solution comprises polyethylene glycol and an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof. The first colon cleansing solution may be hyper-osmotic.

[0129] Preferably, the first colon cleansing solution comprises polyethylene glycol (PEG). The polyethylene glycol (PEG) is disclosed having an average molecular weight of 2000 to 8000, for example 2500 to 4500 Da, for example 2680 to 4020 Da. The first colon cleansing solution of the invention comprise polyethylene glycol having an average molecular weight of 3000 to 4000 Da. For example, the PEG may be PEG 3350 or PEG 4000 as defined in national pharmacopeias. PEG8000 use is also disclosed. Further examples of suitable PEGs recognized in some national pharmacopeias include Macrogols, for example Macrogol 3350 or Macrogol 4000.

[0130] Disclosed are first colon cleansing solutions comprising 175 to 225 g per litre, for example 200g per litre.

[0131] Preferably, the first colon cleansing solution comprises one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof (herein referred to as a "sulphate component"). An alkali metal or alkaline earth metal sulphate may, for example, be selected from sodium sulphate, potassium sulphate and magnesium sulphate. The solution may comprise more than one of sodium sulphate, potassium sulphate and magnesium sulphate, for example all three. Preferably, the sulphate component is or includes sodium sulphate.

[0132] Disclosed are first colon cleansing solutions comprising a sulphate component (for example sodium sulphate) at a concentration of 17 to 19 g per litre (for example sodium sulphate), for example 18g per litre.

[0133] Accordingly, the invention provides a the first colon cleansing solution which may comprise:

1. (i) 175 to 225 g per litre PEG having an average molecular weight of 2500 to 4500 Da.
2. (ii) 17 to 19 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof
3. (iii) optionally one or more electrolytes;
4. (iv) optionally one or more flavouring agents; and
5. (v) optionally one or more sweeteners.

[0134] The first colon cleansing solution may comprise one or more electrolytes. Electrolytes include salts of sodium, potassium, calcium and magnesium, particularly sodium and potassium; and salts of chloride, iodide, bicarbonate and carbonate, particularly chloride. Preferred electrolytes are sodium chloride and potassium chloride. In an embodiment, sodium bicarbonate is not included.

[0135] For example, the first colon cleansing solution may comprise sodium chloride at a concentration of 0.5 to 5.0 g per litre. For example, sodium chloride may be present at a concentration of 1.0 to 4.0 g per litre, for example 1.0 to 3.0 g per litre, for example 1.5 to 3.0g per litre, for example 2.0 to 3.0g per litre; for example 3.0 to 5.0 g per litre, for example 3.5 to 4.5g per litre, for example 4.0 g per litre.

[0136] For example, the first colon cleansing solution may comprise potassium chloride at a concentration of 1 to 10 g per litre. For example, potassium chloride may be present at a concentration of 0.05 to 5.0 g per litre, for example 0.1 to 3.0g per litre, for example 0.2 to 2.0 g per litre, for example 0.5 to 1.5 g per litre, for example 0.5 to 1.1 g per litre; for example 1.5 to 2.5 g per litre, for example 1.8 to 2.2 g per litre, for example 2.0 g per litre.

[0137] In an embodiment, the first colon cleansing solution comprises sodium chloride and potassium chloride. They can be present in the amounts mentioned immediately above. For example, sodium chloride may be present at a concentration of 1.0 to 3.0g per litre and potassium chloride may be present at a concentration of 2.5 to 3.0 g per litre; for example, sodium chloride may be present at a concentration of 3.0 to 5.0g per litre and potassium chloride may be present at a concentration of 0.5 to 1.1 g per litre.

[0138] In an embodiment, the first colon cleansing solution comprises sodium chloride and potassium chloride. They can be present in the amounts mentioned immediately above. For example, sodium chloride may be present at a concentration of 1.5 to 3.0g per litre and potassium chloride may be present at a concentration of 0.2 to 2.0 g per litre; for example, sodium chloride may be present at a concentration of 3.0 to 5.0g per litre and potassium chloride may be present at a concentration of 1.5 to 2.5 g per litre.

[0139] The first colon cleansing solution preferably includes a flavouring agent. The first colon cleansing solution preferably includes a sweetener. Flavouring agents and sweeteners may be as described hereinabove.

[0140] For example, a flavouring for use in in the first colon cleansing solution should preferably mask saltiness, be relatively sweet but not excessively so, and be stable in the composition. A flavouring makes the solutions more palatable and thus aids patient compliance. Preferred flavourings include lemon e.g. Ungerer Lemon (available from Ungerer Limited, Sealand Road, Chester, England CH1 4LP) strawberry e.g. Ungerer Strawberry, grapefruit e.g. Ungerer Grapefruit flavouring powder, blackcurrant e.g. Ungerer Blackcurrant, pineapple e.g. IFF (International Flavours and Fragrances) Pineapple flavouring powder, orange eg Firmenich Orange, and vanilla/lemon and lime e.g. IFF Vanilla and Givaudin Roure

Lemon and Lime Flav-o-lok, fruit punch eg Ungerer fruit punch, citrus punch, mango, and berry. Those and further suitable flavourings are available from International Flavours and Fragrances Inc. (Duddery Hill, Haverhill, Suffolk, CB9 8LG, England), Ungerer & Company (Sealand Road, Chester, England CH1 4LP) or Firmenich (Firmenich UK Ltd., Hayes Road, Southall, Middlesex UB2 5NN). More preferred flavourings are lemon, kiwi, strawberry grapefruit, fruit punch and mango. Fruit punch and mango are especially preferred flavours.

[0141] A particularly preferred flavouring is fruit punch flavour, for example at a level of 0.4 to 3.5g per litre, for example 0.4 to 1.2g per litre, for example 0.938, 1.0 or 3.18g per litre.

[0142] The first cleansing solution preferably includes a sweetener. Preferred sweeteners include aspartame, acesulfame potassium (acesulfame K), sucralose and saccharine, and/ or combinations thereof. For example, the solution may comprise one or both of aspartame and acesulfame potassium (acesulfame K). For example, it may comprise one or both of sucralose and acesulfame potassium (acesulfame K). In a preferred embodiment, the solution comprises aspartame or sucralose, for example sucralose. Preferred sweeteners include aspartame, acesulfame potassium (acesulfame K), sucralose and saccharine, and/ or combinations thereof. For example, compositions of the invention may comprise one or both of aspartame and acesulfame potassium (acesulfame K). For example, compositions of the invention may comprise one or both of sucralose and acesulfame potassium (acesulfame K). In a preferred embodiment, the solution comprises aspartame or sucralose, for example aspartame.

[0143] Alternatively, compositions of the invention can be essentially free from added sweeteners, for example to minimize the number of different components in the compositions.

[0144] A souring agent (for example citric acid) may be present as a taste enhancer. A souring agent is a component that imparts a sourness to a composition. Other souring agents include malic acid, acetic acid, tartaric acid, gluconodeltalactone, phosphoric acid, succinic acid, phytic acid, lactic acid or salts thereof. It may be present at a level of from 0.1 to 3.0 g per litre, for example 0.3 to 2.0 g per litre, for example 0.5 to 2.0g per litre, for example 0.75g, 1.0g, 1.06g, 1.25g or 1.5g per litre. The souring agent (for example citric acid) may be provided in an encapsulated form. The encapsulation provides a coating that isolates the souring agent from other components and from air and moisture prior to its use. Several encapsulated forms of citric acid, or other souring agents, are commercially available. For example, the encapsulation may be with a water-soluble coating.

[0145] The amount of sweetener required depends on the nature and strength of the sweetener being considered. Typically, it is 0.10 to 4 g per litre. For example, the sweetener may be sucralose at 0.1 to 3.0g per litre, for example 0.3 to 2.0 g per litre, for example 0.5 to 2.0g per litre, for example 0.5 to 1.3g per litre for example 0.63g, 0.80g, 1.0g or 1.58g per litre.

[0146] The first cleansing solution may include one or more further optional components. Such components may be as set out above in section 3b).

[0147] In an embodiment, the first colon cleansing solution has a volume of from 400 to 600ml (for example 500ml), and contains the quantities of solutes described in the section immediately above. For example the volume may be 16 or 17 US fluid ounces. For example, the invention provides colon cleansing solution comprising :

1. (i) 175 to 220 g per litre PEG having an average molecular weight of 2500 to 4500 Da.
2. (ii) 17 to 19 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof
3. (iii) 3.0 to 5.0 g per litre sodium chloride, and 1.5 to 2.5 g per litre potassium chloride;
4. (iv) optionally one or more flavouring agents; and
5. (v) optionally one or more sweeteners.

[0148] Such a solution has a smaller volume than cleansing solutions that are generally used.

[0149] In an embodiment, the first colon cleansing solution is provided in a volume of from 300ml up to 1200ml. For example, the first solution may have a volume in a range with a lower limit of 300ml, 400ml, 500ml, 600ml or 700ml. Preferably, the lower limit is 500ml, 600ml or 700ml. The volume may be in a range with an upper limit of 1200ml, 1100ml, 1000ml, 900ml or 800ml. For example the volume may be in the range 400ml to 1100ml, for example 500ml to 1000ml, for example 600ml to 900ml, for example 700ml to 800ml. For example, the first colon cleansing solution is provided in a volume of 750ml. For example the volume may be in the range 400ml to 600ml. For example, the first colon cleansing solution is provided in a volume of 500ml. For example it may be in a volume of 16 or 17 US fluid ounces. The most appropriate volume will depend on the exact components of the solution and the amounts in which they are present. In general, for a solution of higher osmotic strength, a smaller volume will be required.

[0150] The first cleansing solution may, for example, have a measured osmolality in the range 200 to 2000 mOsmol/kg, 200 to 1500 mOsmol/kg. In a preferred embodiment, it is hyper-osmotic. It may, for example have a measured osmolality in the range 320 to 1500 mOsmol. For example, the measured osmolality of the first cleansing solution is in the range 330 to 1200 mOsmol/kg, for example 340 to 1000 mOsmol/kg, for example 350 to 800 mOsmol/kg, for example 350 to 700 mOsmol/kg. For example, the solutes in the solution may have a V(350) value of from 800 to 1600ml, for example from 1000 to 1400ml, for example from 1150 to 1250ml, and be in a volume of 400 to 600ml, for example 500ml.

[0151] The invention further provides a composition optionally presented in two or more parts for the preparation of a first colon cleansing solution. For example the composition may comprise:

1. (i) 87.5 to 110 g PEG having an average molecular weight of 2500 to 4500 Da.
2. (ii) 7.5 to 10 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof

3. (iii) 1.5 to 2.5g sodium chloride and 0.75 to 1.25g potassium chloride;
4. (iv) optionally one or more flavouring agents; and
5. (v) optionally one or more sweeteners.

[0152] For example the composition may comprise:

1. (i) 100 g PEG having an average molecular weight of 3000 to 4000 Da.
2. (ii) 9.0 g sodium sulphate
3. (iii) 2.0g sodium chloride and 1.0g potassium chloride;
4. (iv) optionally one or more flavouring agents; and
5. (v) optionally one or more sweeteners.

[0153] For example, the flavouring and sweetener may be 0.469g fruit punch flavouring, 0.476g sucralose and 0.792g citric acid. For example, the flavouring and sweetener may be 0.500g fruit punch flavouring, 0.40g sucralose and 0.75g citric acid. For example, the flavouring and sweetener may be 1.43g mango flavouring, 0.79g sucralose and 1.74g citric acid. For example, the flavouring and sweetener may be 1.59g fruit punch flavouring, 0.79g sucralose and 1.74g citric acid. Citric acid may optionally be packaged separately from the other components.

[0154] Particular first solutions S1 and S2, and particular second solutions T1 and T2 are described in the examples section below. In a preferred aspect of the present invention, there is provided a method of cleansing the colon of a subject comprising (or consisting essentially of):

administering to the subject a cleansing solution of S2 as set forth herein;

administering to the subject a cleansing solution of T1 as set forth herein.

[0155] In preferred embodiments of this aspect of the invention, the cleansing solution of S2 is administered to the subject before the cleansing solution of T1 is administered. It is particularly preferred that S2 is administered to the subject and then, following a time interval (such as disclosed herein), T1 is administered to the subject. In further preferred embodiments of this aspect of the invention, additional fluid (such as clear fluid) is administered to the subject in conjunction with S2 and/or T1. For example, additional clear fluid (such as 500ml or thereabout, or 1000ml or thereabout) is administered to the subject following administration of S2 and/or T1. Alternatively, additional clear fluid is administered to the subject during administration of S2 and/or T1. In typical embodiments, the cleansing solution of S2 and/or T1 is self-administered.

7. Use of sweetener in colon cleansing solution

[0156] It has been found by the current inventors that a sulphate-containing colon cleansing solution that contains a souring agent (for example citric acid) and sucralose is particularly palatable.

[0157] Further, the invention provides a method for improving the palatability of a sulphate-containing colon cleansing solution comprising including in the solution 0.1 to 3.0g per litre sucralose and 0.1 to 4.0g per litre of souring agent, for example 0.1 to 3.0 g per litre of souring agent, for example citric acid. The invention provides a method for diminishing the poor taste of a sulphate-containing colon cleansing solution comprising including in the solution 0.1 to 3.0g per litre sucralose and 0.1 to 4.0gof souring agent, for example 0.1 to 3.0 g per litre of souring agent, for example citric acid.

[0158] It is postulated that the improved palatability is associated with a reduced perceived saltiness of the solutions. The invention thus provides a method for reducing the perceived saltiness of a sulphate-containing colon cleansing solution comprising including in the solution 0.1 to 3.0g per litre sucralose and 0.1 to 4.0g per litre of souring agent, for example 0.1 to 3.0 g per litre of souring agent, for example citric acid. "Reduction" here is taken to mean as compared with an equivalent solution without the sucralose and souring agent.

[0159] A souring agent may be selected from citric acid, malic acid, acetic acid, tartaric acid, gluconodeltalactone, phosphoric acid, succinic acid, phytic acid, lactic acid or salts thereof. For example, the souring agent may be citric acid. It may be present at a level of from 0.1 to 4.0g per litre, for example 0.1 to 3.0 g per litre, for example 0.3 to 2.0 g per litre, for example 0.5 to 2.0g per litre, for example 0.75g, 1.0g, 1.06g, 1.25g or 1.5g per litre. For example, it may be at a level of 3.0 to 4.0g per litre, for example 3.48g per litre. Citric acid, or another souring agent, may be provided in an encapsulated form. The encapsulation provides a coating that isolates the souring agent from other components and from air and moisture prior to its use. Several encapsulated forms of citric acid, or other souring agents, are commercially available. For example, the encapsulation may be with a water-soluble coating.

[0160] The sucralose may, for example be present at a level of 0.1 to 3.0g per litre, for example 0.3 to 2.0 g per litre, for example 0.5 to 2.0g per litre, for example 0.5 to 1.3g per litre for example 0.63g, 0.80g, or 1.0g per litre. For example, it may be at a level of 1.58g per litre.

[0161] When sucralose and citric acid are used, a particularly preferred flavouring is fruit punch flavour, for example at a level of 0.4 to 1.2g per litre, for example 0.625g per litre or 1.0g per litre.

[0162] There is also provided a composition for the preparation of such a solution, for example by admixture with water.

8. Kits

b) kits providing treatments according to the invention

[0163] As set out above in section 6), the invention provides various split-dose treatments for colon cleansing in which the subject takes two different agents. The invention thus provides a kit comprising:

- a first colon cleansing agent, and
- a second colon cleansing agent,

the second colon cleansing agent being a solution of the first or second aspect of the invention described above.

[0164] The invention provides a kit comprising:

- a first colon cleansing agent, and
- a second colon cleansing agent,

the second colon agent solution being a solution in water of:

1. a) 300 to 800 mmol per litre ascorbate anion provided by a mixture of
    1. (i) ascorbic acid and
    2. (ii) one or more salts of ascorbic acid

   the components (i) and (ii) being present in a molar ratio of from 1:4.5 to 1:7.0; and
2. b) optionally 10 to 200 g per litre polyethylene glycol.

[0165] The invention also provides a kit comprising:

- a first colon cleansing agent, and
- a second colon cleansing agent,

the second colon cleansing agent being a solution in water of:

1. a) 360 to 440 mmol per litre ascorbate anion provided by one or more salts of ascorbic acid; and
2. b) optionally 10 to 200 g per litre polyethylene glycol;

the solution being essentially free from ascorbic acid.

[0166] The first agent is different from the second.

[0167] A kit of the invention may provide compositions for the preparation of the colon cleansing solutions. The invention thus further provides a kit comprising:

1. A) a first component, being a composition, optionally presented in two or more parts for the preparation of a first colon cleansing solution as described above by admixture with water; and
2. B) a second component, being a composition, optionally presented in two or more parts for the preparation of a second colon cleansing solution by admixture with water, the second colon cleansing solution being a solution as described hereinabove in relation to solutions and uses of the first or second aspects of the invention as set out in sections 2 to 5.

[0168] Preferably, the first solution is of different composition from the second.

[0169] The first component may be a composition for the preparation of a solution as set out in section 6b) above. The first component preferably comprises 90 to 112.5 g, for example 100 g PEG.

[0170] Preferably, the first component comprises 9g of sodium sulphate.

[0171] Preferably, the first component comprises sodium chloride in an amount of 0.375 to 3.75 g. For example, sodium chloride may be present in an amount of 0.75 to 3.0 g, for example 0.75 to 2.25 g, for example 1.125 to 2.25 g, for example 1.5 to 2.25 g, for example 2.0g.

[0172] For example, the first component comprises potassium chloride in an amount of 0.75 to 7.5 g. For example, potassium chloride may be present in an amount of 0.0375 to 3.75 g, for example 0.075 to 2.25 g, for example 0.15 to 1.5 g, for example 0.375 to 1.125 g, for example 0.375 to 0.825 g, for example 1.0g.

[0173] In an embodiment, the first component comprises sodium chloride and potassium chloride. They can be present in the amounts mentioned immediately above. For example, sodium chloride may be present in an amount of 1.125 to 2.25 g and potassium chloride may be present in an amount of 0.15 to 1.5 g; for example 2.0g sodium chloride and 1.0g potassium chloride.

[0174] The second component of the kit of compositions of the invention is preferably a composition for the preparation of a solution of the first or second aspect of the invention as described hereinabove in sections 3 or 5.

[0175] Accordingly, the kit may comprise:

1. A) a first component, being a composition optionally presented in two or more parts for

the preparation of a first colon cleansing solution comprising :

1. (i) 87.5 to 110 g PEG having an average molecular weight of 2500 to 4500 Da.
2. (ii) 7.5 to 10 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof
3. (iii) 1.5 to 2.5g sodium chloride and 0.75 to 1.25g potassium chloride;
4. (iv) optionally one or more flavouring agents; and
5. (v) optionally one or more sweeteners,

and

2. B) a second component, being a composition optionally presented in two or more parts for the preparation of a second colon cleansing solution, comprising

a)

1. (i) 6.0 to 10g ascorbic acid and
2. (ii) 40 to 60g sodium ascorbate

the components (i) and (ii) being present in a weight ratio of from 1:5063 to 1:7.875;

b) 30 to 50g PEG having an average molecular weight of 3000 to 4000 Da;

c) 1.5 to 4g sodium chloride and 0.5 to 3.5g potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

[0176] In an embodiment of a kit, in component B) the ascorbate component a) is packaged separately from the PEG component b). The remaining elements of component B) may be packaged together with the PEG component.

[0177] For example, a kit may comprise:

1. A) a first component, being a composition optionally presented in two or more parts for the preparation of a first colon cleansing solution comprising :
   1. (i) 100 g PEG having an average molecular weight of 3000 to 4000 Da.
   2. (ii) 9.0 g sodium sulphate
   3. (iii) 2.0g sodium chloride and 1.0g potassium chloride;
   4. (iv) optionally one or more flavouring agents; and
   5. (v) optionally one or more sweeteners,

   and
2. B) a second component for the preparation of a second colon cleansing solution, comprising

a)

1. (i) 7.54g ascorbic acid and

2. (ii) 48.11g sodium ascorbate

b) 40g PEG having an average molecular weight of 3000 to 4000 Da;

c) 3.20g sodium chloride and 1.20g potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners;

whereby component a) is packaged in a first compartment and components b), c) e) and f) are packaged in a second compartment.

[0178] For example, the flavouring and sweetener in the first component may be 0.469g fruit punch flavouring, 0.476g sucralose and 0.792g citric acid. For example, the flavouring and sweetener may be 0.500g fruit punch flavouring, 0.40g sucralose and 0.75g citric acid. For example, the flavouring and sweetener may be 1.43g mango flavouring, 0.79g sucralose and 1.74g citric acid. For example, the flavouring and sweetener may be 1.59g fruit punch flavouring, 0.79g sucralose and 1.74g citric acid. Citric acid may optionally be packaged separately from the other components.

[0179] For example, the flavouring and sweetener in the second component may be 0.60g orange flavour and 1.93g aspartame. For example, the flavouring and sweetener may be 1.60g citrus flavour and 0.875g aspartame. For example, the flavouring and sweetener may be 2.10g orange grapefruit flavour and 0.875g aspartame.

[0180] In an embodiment of a kit of the invention, in component B) the ascorbate component a) is packaged separately from the PEG component b). The remaining elements of component B) may be packaged together with the PEG component.

[0181] For example, the flavouring and sweetener in the first component may be 0.469g fruit punch flavouring, 0.476g sucralose and 0.792g citric acid. For example, the flavouring and sweetener may be 0.500g fruit punch flavouring, 0.40g sucralose and 0.75g citric acid. For example, the flavouring and sweetener may be 1.43g mango flavouring, 0.79g sucralose and 1.74g citric acid. For example, the flavouring and sweetener may be 1.59g fruit punch flavouring, 0.79g sucralose and 1.74g citric acid. Citric acid may optionally be packaged separately from the other components.

[0182] For example, the flavouring and sweetener in the second component may be 0.80g orange flavour and 1.10g aspartame. For example, the flavouring and sweetener may be 1.60g lemon/lime flavour and 1.625g aspartame. For example, the flavouring and sweetener may be 2.15g orange grapefruit flavour and 1.625g aspartame.

[0183] Preferably, the kit further comprises instructions for use. In an embodiment, a kit of the

invention has instructions that instruct the user of the volume to which each component is to be made up with water. For example, the specified volume of water for each solution is less than one litre. For example, the specified volume for the first component may be 300ml to 1200ml, for example 600ml to 900ml, for example 750ml; for example it may be a volume of 25 or 26 US fluid ounces, for example 400 to 600ml, for example 500ml. For example it may be a volume of 16 or 17 US fluid ounces. For example, the specified volume for the second component may be from 250ml to 1000ml, for example 400ml to 700ml, for example 500ml. For example it may be a volume of 16 or 17 US fluid ounces. Further volumes that may be specified in the instructions are the volumes set out hereinabove in relation to the methods of the invention.

[0184] In general, the instructions specify that the first and second solutions are to be ingested in succession with a time interval between them. In an embodiment, the instructions specify that the first cleansing solution is ingested first followed, after a time interval (for example the time between an evening and the following morning) by ingestion of the second cleansing solution. The time interval is preferably as described above in relation to the methods of the invention. The instructions may specify that the components in the kit be made up into solutions and then taken in accordance with the description set out above in section 6 for the first solution and sections 3c) and 5c) for the second solution.

[0185] For example, components A) and B) may be in dry powder, granular or other dry form. They may alternatively be in the form of concentrates or slurries. Components A) and B) may be in the same or different physical forms. Components within A) and B) may be in the same or different physical forms. For example, one or both of components A) and B) are dry powders. A portion of either or each of components A) and B) may be in the form of one or more solid tablets or capsules.

[0186] It is convenient for the patient for a kit of the invention to be provided in the form of, for example, a box. In a kit of the invention the first and/or second components may each contained in one or more containers. In particular, the second component may be contained in more than one container. For example, if the second component comprises both ascorbic acid and PEG then the ascorbic acid and PEG may be contained in separate containers. The other constituents of the second component (for example one or more of sodium chloride, potassium chloride and sodium sulphate) may be in either of the separate containers. For example, they may be in the container containing the PEG.

[0187] If a flavouring component is present in the first or second solution, then in a kit of the invention, the flavouring component for the relevant solution may be provided in a separate container from the other constituents of that solution.

[0188] Examples of suitable containers include tubs, bags and sachets. A preferred container is a sachet.

[0189] In one embodiment, the composition of the invention can be provided in a multi-

chambered container, for example of the type disclosed in WO2012/105524, as described above in section 8a).

[0190] In one embodiment, a kit comprises:

A) a first sachet comprising a first composition for the preparation of the first cleansing solution;

B1) a second sachet;

B2) a third sachet;

wherein the second and third sachets together provide a composition for the preparation of the second cleansing solution.

[0191] For example, in a kit of the invention as mentioned immediately above:

A) the first sachet comprises polyethylene glycol and/or sodium sulphate;

B1) the second sachet comprises one or more components selected from polyethylene glycol, one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof and electrolytes; and

B2) the third sachet comprises one or more salts of ascorbic acid and, if appropriate, ascorbic acid; the contents of sachets (B1) and (B2) together providing the components for the second cleansing solution.

[0192] For example, in a further embodiment of a kit of the invention, rather than being provided within a first sachet (A) with the PEG, some or all of the sulphate(s), electrolytes, flavouring agents and sweeteners are provided in the form of a tablet or capsule. In a further embodiment of a kit of the invention, rather than being provided within a second or third sachet (B1 or B2) with the PEG, ascorbic acid or ascorbate component, some or all of the sulphate(s), electrolytes, flavouring agents and sweeteners are provided in the form of a tablet or capsule.

[0193] A kit may contain one treatment, for example a cleansing treatment, or several treatments. A treatment generally comprises one dose of the first cleansing solution (or components for preparing the first cleansing solution) and one dose of the second cleansing solution (or components for preparing the first cleansing solution). In a kit of the invention, preferably the first component comprises one dose of the first cleansing solution, and the second component comprises one dose of the second cleansing solution.

[0194] A kit of the invention may be for use in a method of cleansing the colon comprising:

- the subject taking an effective amount of a first colon cleansing solution as described herein; and then
- the subject taking an effective amount of a second colon cleansing solution as described

herein.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO2004037292A [0005] [0005]
- WO2013001315A [0053]
- WO2009052256A [0058]
- WO2012105524A [0189]

Non-patent literature cited in the description

- **HARIDIA**J. Microbiol., 2011, vol. 49, 4663-8 [0061]

Patentkrav

1. Tyktarmsrensningsopløsning der omfatter:

(i) 175 til 225 g pr. liter PEG med en gennemsnitsmolekylvægt på 2500 til 4500 Da;
ii) 17 til 19 g pr. liter af et eller flere alkalimetalsulfater, jordalkalimetalsulfater eller en blanding deraf;
(iii) eventuelt en eller flere elektrolytter;
(iv) eventuelt et eller flere smagsstoffer; og
(v) eventuelt et eller flere sødestoffer.

2. Tyktarmsrensningsopløsningen ifølge krav 1, hvilken opløsning administreres med et volumen på 400 til 800 ml.

3. Tyktarmsrensningsopløsningen ifølge krav 1, hvilken opløsning administreres med et volumen på 400 til 600 ml.

4. Tyktarmsrensningsopløsning ifølge et hvilket som helst af de foregående krav der yderligere omfatter 3,0 til 5,0 g pr. liter natriumchlorid og 1,5 til 2,5 g pr. liter kaliumchlorid.

5. Tyktarmsrensningsopløsning ifølge et hvilket som helst af de foregående krav der yderligere omfatter et syrningsmiddel, for eksempel citronsyre.

6. Tyktarmsrensningsopløsning ifølge et hvilket som helst af de foregående krav, hvor sødemidlet er sucralose.

7. Tyktarmsrensningsopløsning ifølge et hvilket som helst af de foregående krav, hvor smagsstoffet er frugtpunchsaroma.

8. Sammensætning der eventuelt præsenteres i to eller flere dele, til fremstilling af en tyktarmsrensningsopløsning ifølge krav 1, der omfatter:

(i) 87,5 til 110 g PEG med en gennemsnitsmolekylvægt på 2500 til 4500 Da;
(ii) 7,5 til 10 g af et eller flere alkalimetalsulfater, jordalkalimetalsulfater eller en blanding deraf;
(iii) 1,5 til 2,5 g natriumchlorid og 0,75 til 1,25 g kaliumchlorid;
(iv) eventuelt et eller flere smagsstoffer; og
(v) eventuelt et eller flere sødestoffer.

9. Sammensætningen ifølge krav 8 der omfatter:

(i) 100 g PEG med en gennemsnitsmolekylvægt på 3000 til 4000 Da;
(ii) 9,0 g natriumsulfat;
(iii) 2,0 g natriumchlorid og 1,0 g kaliumchlorid;
(iv) eventuelt et eller flere smagsstoffer; og
(v) eventuelt et eller flere sødestoffer.

10. Kit der omfatter:

- en første tyktarmsrensningsopløsning og
- en anden tyktarmsrensningsopløsning,

hvilken første tyktarmsrensningsopløsning er ifølge et hvilket som helst af kravene 1 til 9, og den anden tyktarmsrensningsopløsning omfatter:

a) 300 til 800 mmol pr. liter ascorbatanion der er tilvejebragt af en blanding af:
(i) ascorbinsyre og
(ii) et eller flere salte af ascorbinsyre,
hvor komponenterne (i) og (ii) er til stede i et molforhold på fra 1:4,5 til 1:7,0; og

b) 10 til 200 g pr. liter polyethylenglycol.

11. Kittet ifølge krav 10, hvor den anden rensningsopløsning omfatter en eller flere af følgende:

(a) det ene eller de nævnte flere salte af ascorbinsyre er valgt blandt: natriumascorbat, kaliumascorbat, magnesiumascorbat og calciumascorbat eller en blanding deraf;
(b) ascorbatanionen i en koncentration på 300-700 mmol pr. liter, for eksempel 350-650 mmol pr. liter, for eksempel 450-600 mmol pr. liter;
(c) molforholdet mellem komponenterne (i) og (ii) er fra 1:4,75 til 1:6,75; mere fortrinsvis fra 1:5,0 til 1:6,0; for eksempel fra 1:5,40 til 1:5,80; for eksempel 15:85;
(d) opløsningen omfatter 60 til 140 g/liter ascorbatkomponent, for eksempel 80 til 130 g/liter, for eksempel 80 til 120 g/liter, for eksempel 100 til 120 g/liter; og/eller
(e) 12 til 20 g/liter ascorbinsyre og 80 til 120 g/liter natriumascorbat.

12. Kit ifølge et hvilket som helst af kravene 10 til 11, hvor den anden rensningsopløsning omfatter en eller flere af følgende:

(a) polyethylenglycol der har en gennemsnitsmolekylvægt på 2000 til 8000, for eksempel 2500 til 4500 Da, for eksempel 2680 til 4020 Da, for eksempel 3000 til 4000 Da;
(b) 20 til 160 g pr. liter PEG, for eksempel 40 til 120 g pr. liter, for eksempel 60 til 100 g pr. liter, for eksempel 80 g pr. liter;
(c) natriumchlorid i en koncentration på 3 til 8 g pr. liter, for eksempel 4 til 7 g pr. liter; for eksempel 5,6 g pr. liter eller 6,4 g pr. liter;
(d) kaliumchlorid i en koncentration på 1 til 10 g pr. liter, for eksempel en koncentration på 1 til 7 g pr. liter, for eksempel 1,5 til 5 g pr. liter, for eksempel 1,5 til 3 g pr. liter, for eksempel 2,0 til 2,8 g per liter; for eksempel 2,4 g pr. liter eller 2,6 g pr. liter; og/eller

e) natriumsulfat, kaliumsulfat eller magnesiumsulfat i en koncentration på 2 til 20 g pr. liter, for eksempel 5 til 15 g pr. liter, for eksempel 8 til 15 g pr. liter, for eksempel 10 til 14 g pr. for eksempel 12 g pr. liter.

13. Kit ifølge et hvilket som helst af kravene 10 til 12, hvor den anden rensningsopløsning omfatter en eller flere af følgende:

a) i det væsentlige fri for alkalimetalsulfater og jordalkalimetalsulfater;
(b) et smagsstof;
(c) et sødemiddel.
d) smagsstof af aspartam og appelsin; og/eller
(e) 0,5 til 4 g pr. liter aspartam, for eksempel 2,5 til 4,0 g pr. liter, for eksempel 3,0 g pr. liter, for eksempel 3,86 g pr. liter; og 0,2 til 1,8 g pr. liter appelsinsmagsstof.

14. Kit ifølge et hvilket som helst af kravene 10 til 13, hvor den anden rensningsopløsning omfatter:

a) 300 til 800 mmol pr. liter ascorbatanion der er tilvejebragt af en blanding af:
(i) ascorbinsyre og
(ii) et eller flere salte af ascorbinsyre,
hvor komponenterne (i) og (ii) er til stede i et molforhold på fra 1:4,5 til 1:7,0;

b) 10 til 200 g pr. liter PEG med en gennemsnitsmolekylvægt på 3000 til 4000 Da;
c) natriumchlorid og kaliumchlorid;
e) et eller flere smagsstoffer; og
f) et eller flere sødestoffer.

15. Kit ifølge et hvilket som helst af kravene 10 til 14, hvor nogle af alle komponenterne i den anden rensningsopløsning, bortset fra ascorbatkomponenten og PEG'en, er tilvejebragt separat fra opløsningen, for eksempel i en tablet eller kapsel.

16. Kit der omfatter sammensætninger til blanding med vand, hvilke sammensætninger er til fremstilling af den første og anden opløsning, der er angivet i et hvilket som helst af kravene 1 til 15.

17. Kit der omfatter sammensætninger til blanding med vand ifølge krav 16, hvilket kit omfatter:

A) en første komponent der er en sammensætning, som eventuelt præsenteres i to eller flere dele, til fremstilling af en første tyktarmsrensningsopløsning der omfatter:

(i) 100 g PEG med en gennemsnitsmolekylvægt på 3000 til 4000 Da;

(ii) 9,0 g natriumsulfat;
(iii) 2,0 g natriumchlorid og 1,0 g kaliumchlorid;
(iv) eventuelt et eller flere smagsstoffer; og
v) eventuelt et eller flere sødestoffer

og

B) en anden komponent til fremstilling af en anden tyktarmsrensningsopløsning der omfatter:

a)
(i) 7,54 g ascorbinsyre og
(ii) 48,11 g natriumascorbat;
b) 40 g PEG med en gennemsnitsmolekylvægt på 3000 til 4000 Da;
c) 3,20 g natriumchlorid og 1,20 g kaliumchlorid;
e) et eller flere smagsstoffer; og
f) et eller flere sødestoffer;

hvor komponent (a) er pakket i et første rum og komponenter (b), (c) (e) og (f) er pakket i et andet rum.

18. Kit ifølge et hvilket som helst af kravene 10 til 17 til anvendelse i en fremgangsmåde til rensning af tyktarmen der omfatter:

- at individet tager en effektiv mængde af en første tyktarmsrensningsopløsning som beskrevet i et hvilket som helst af kravene 1 til 7; og så
- at individet tager en effektiv mængde af en anden tyktarmsrensningsopløsning som defineret i et hvilket som helst af kravene 10 til 17.

19. Tyktarmsrensningsopløsning ifølge et hvilket som helst af kravene 1 til 9 til anvendelse i en fremgangsmåde til rensning af tyktarmen hos et individ.

20. Fremgangsmåde til at forbedre smagen af en sulfatholdig tyktarmsrensningsopløsning ifølge krav 1 eller krav 2, hvilken fremgangsmåde omfatter at inkludere 0,1 til 3,0 g pr. liter sucralose og 0,1 til 4,0 g pr. liter syrningsmiddel, for eksempel citronsyre, i opløsningen.

21. Fremgangsmåden ifølge krav 20, hvor sucralosen er inkluderet i et niveau på 0,3 til 2,0 g pr. liter, for eksempel 0,5 til 2,0 g pr. liter, for eksempel 0,5 til 1,3 g pr. liter, for eksempel 0,63 g, 0,80 g eller 1,0 g pr. liter for eksempel inkluderet i et niveau på 1,58 g pr. liter.

22. Fremgangsmåde ifølge krav 20 eller krav 21, hvor syrningsmidlet er valgt blandt: citronsyre, æblesyre, eddikesyre, vinsyre, gluconodeltalacton, phosphorsyre, ravsyre, phytinsyre, mælkesyre eller salte deraf.

DRAWINGS

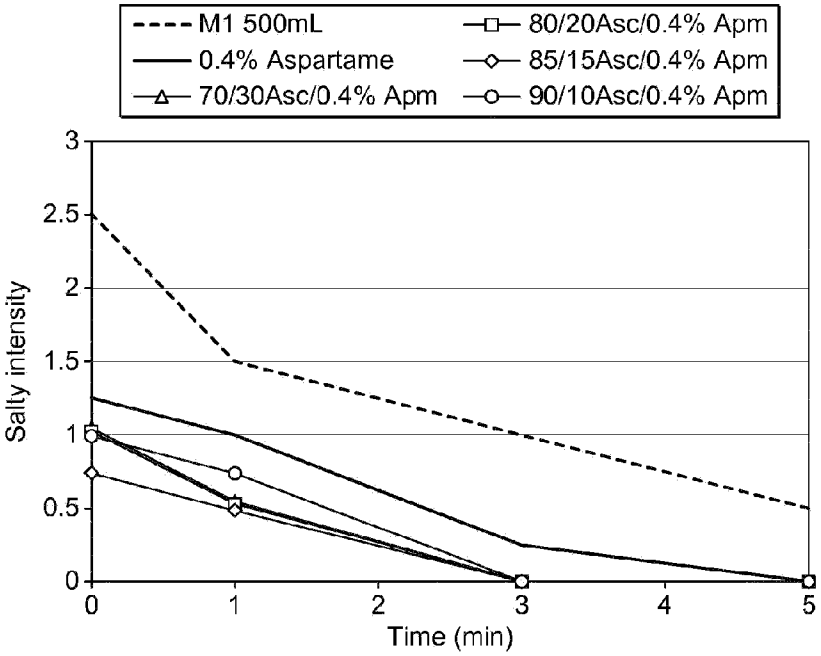

FIG. 1

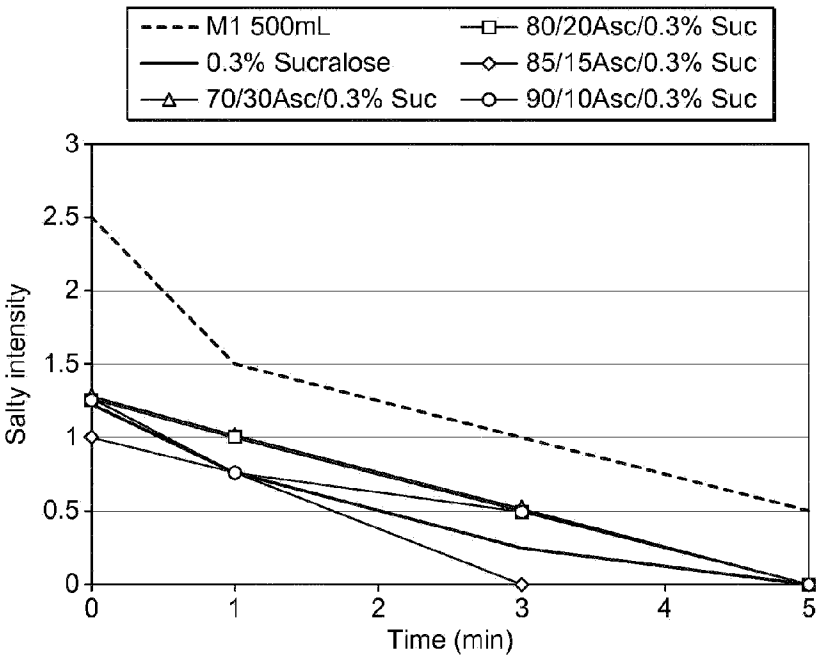

FIG. 2

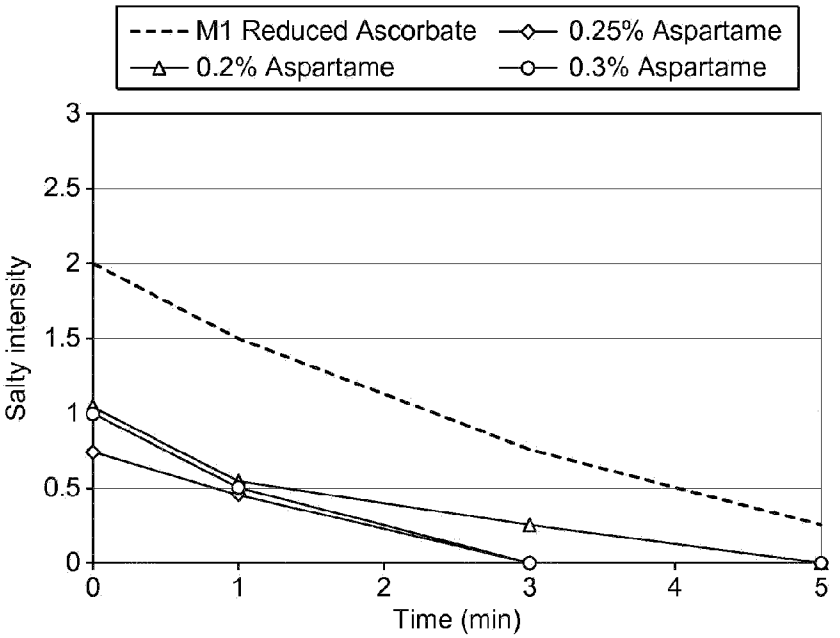
M1 Reduced Ascorbate
0.25% Aspartame
0.2% Aspartame
0.3% Aspartame
Salty intensity
Time (min)
0
0.5
1
1.5
2
2.5
3
0
1
2
3
4
5

FIG. 3

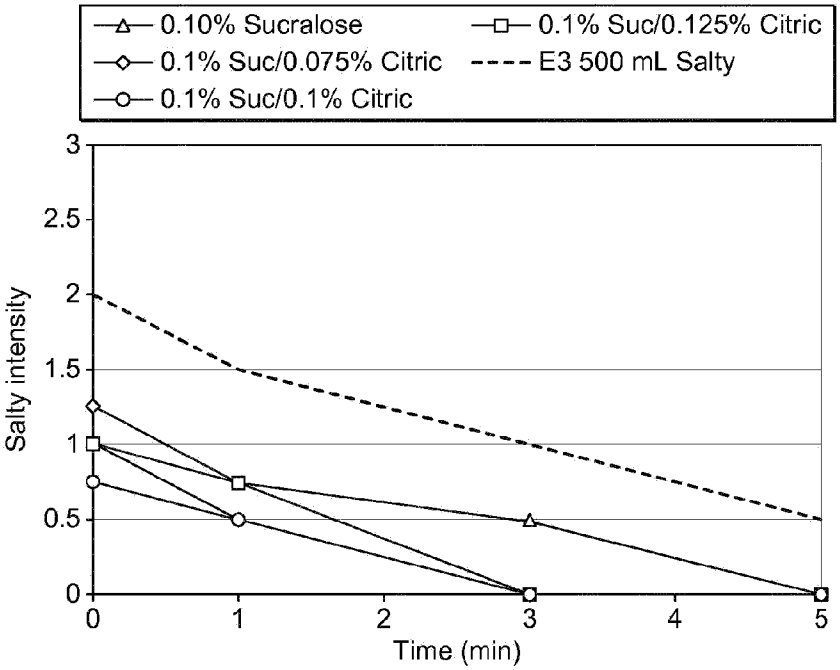
0.10% Sucralose
0.1% Suc/0.125% Citric
0.1% Suc/0.075% Citric
E3 500 mL Salty
0.1% Suc/0.1% Citric
Salty intensity
Time (min)
0
0.5
1
1.5
2
2.5
3
0
1
2
3
4
5

FIG. 4