# Colon Cleansing Compositions

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.

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.

Intestinal lavage, in which a large volume of an 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.

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.

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, a significant benefit when compared to taking 4 litres of previous solutions.

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 optionally 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").

Despite the advances that have been made, all 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.

When comparing the pharmacokinetic profiles of the components of the MOVIPREP solution (ascorbate component, sodium sulphate, PEG 3350 and electrolytes) in subjects who had taken the solution in the "evening before" regimen with the pharmacokinetic profiles in subjects who had taken the solution in the "split-dose" regimen in a clinical study, the present inventors found that a surprisingly high proportion of the ascorbate component of the first dose of the "split-dose" regimen was absorbed into the subjects' circulations. The proportion of the ascorbate component that was found to be absorbed into the circulation was then excreted in the subjects' urine over time, rather than being expelled in faeces. Whilst this absorption into the circulation is not harmful to the subject, it does reduce the osmotic strength of the solution, and hence it reduces the solution's ability to cleanse the colon. It is also wasteful of the component. The finding was surprising in view of the commonly accepted view in the literature that a maximum of 3g of ascorbic acid can be absorbed in the intestines per day (Hornig, D. *et al.*, Int. J. Vit. Nutr. Res., 1980, **50**, 309). Ascorbate-containing colon cleansing solutions have to date been formulated on that basis.

Summary

In one aspect, the present invention refers to a colon cleansing solution comprising:
a) 60 to 150 g/ litre of an ascorbate component, the ascorbate component being ascorbic acid, one or more salts of ascorbic acid, or a mixture of ascorbic acid and one or more salts of ascorbic acid; and
b) 10 to 200 g per litre polyethylene glycol.

In another aspect, the present invention refers to a composition, optionally presented in two or more parts, for admixture with water to provide a solution of the present invention.

In another aspect, the present invention refers to a composition for admixture with water for the preparation of a colon cleansing solution of the present invention, comprising the following components in the following weight ratios:
a) ascorbate anion provided by ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof:

0.82 to 10.0 parts

b) polyethylene glycol: 1.0 part.

In another aspect, the present invention refers to a kit comprising:

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

the second colon cleansing solution being the solution of the present invention in water.

In another aspect, the present invention refers to a kit comprising:

A) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with water; and

B) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with water;

and optional instructions for use,

the second colon cleansing solution being the solution of the present invention in water,

the first solution being different from the second.

In another aspect, the present invention refers to a solution of the present invention for use in cleansing the colon of a subject in combination with a colon cleansing solution comprising:

(i) 130 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 8.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof.

In another aspect, the present invention refers to a solution of the present invention for use in cleansing the colon of a subject in combination with a colon cleansing solution consisting essentially of water and:

(i) 130 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 8.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii 1) 1.0 to 3.0 g/L sodium chloride;

(iii 2) 0.5 to 1.5 g/L potassium chloride;

(iv) one or more flavouring agents;

(v) one or more sweeteners.

In another aspect, the present invention refers to a solution that is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, for use in a method of cleansing the colon of a subject comprising:

- administering to the subject an effective amount of a first cleansing solution; and then after a time interval

- administering to the subject an effective amount of a second cleansing solution,

wherein the second cleansing solution is a solution of the present invention, is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution.

In another aspect, the present invention refers to a kit comprising:

- a first colon cleansing solution; and

- a second colon cleansing solution,

wherein the second colon cleansing solution is a solution of the present invention, is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first colon cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion in the first colon solution than is present in the second colon cleansing solution.

In another aspect, the present invention refers to a kit comprising:

a) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with water; and

b) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with water,

and instructions for use that specify the volume to which each component is to be made up with water,

wherein the second colon cleansing solution, when made up to the instructed specified volume with water, is a solution of the present invention, is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first colon cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains, when made up to the instructed specified volume with water, ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing, a lower concentration of ascorbate anion in the first colon solution than in the second colon cleansing solution.

Detailed Description

The invention thus provides, in a first aspect, a colon cleansing solution comprising:
a) 60 to 150g/ litre of an ascorbate component, the ascorbate component being ascorbic acid, one or more salts of ascorbic acid, or a mixture of ascorbic acid and one or more salts of ascorbic acid; and
b) 10 to 200 g per litre polyethylene glycol.

The solution of the invention is a surprisingly effective colon cleansing solution as measured by stool output, providing satisfactory clearance of stools from the colon with ingestion of a smaller total volume of solution than with the standard 2 or 4 litre solutions of the prior art.

The ascorbate component is ascorbic acid, one or more salts of ascorbic acid, or a mixture of ascorbic acid and one or more salts of ascorbic acid. Suitable salts 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. In an example, the ascorbate component is ascorbic acid, one or more salts of ascorbic acid selected from sodium ascorbate, potassium ascorbate, magnesium ascorbate and calcium ascorbate, or a mixture thereof. Particularly preferred salts of ascorbic acid are magnesium ascorbate and sodium ascorbate, for example sodium ascorbate. In one example, the solution comprises ascorbic acid and one or more salts of ascorbic acid (and preferably no further ascorbate), for example ascorbic acid and sodium ascorbate (and preferably no further ascorbate), or ascorbic acid and magnesium ascorbate (and preferably no further ascorbate).

A solution of the invention comprises 60 to 150g/litre of the ascorbate component, for example 60 to 120g/litre, for example 80 to 120g/litre, for example 100 to 120g/litre.

In an embodiment, the ascorbate component consists essentially of sodium ascorbate alone. For example, it may be present in an amount as mentioned immediately above.

In an alternative embodiment, the ascorbate component comprises (or consists essentially of) sodium ascorbate and ascorbic acid. For example, they may be present in a total amount as mentioned immediately above. They may be in a weight ratio of sodium ascorbate : ascorbic acid from 1:10 to 10:1, for example 2:8 to 8:2, for example 3:7 to 7:3, for example 1.4:1 to 1.8:1.

In an alternative embodiment, the ascorbate component comprises (or consists essentially of) of sodium ascorbate and magnesium ascorbate. For example, they may be present in a total amount as mentioned immediately above. They may be in a weight ratio of sodium ascorbate : magnesium ascorbate from 1:10 to 10:1, for example 2:8 to 8:2, for example 3:7 to 7:3, for example 1.8:1 to 1.4:1.

The 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 3000 to 4000 Da. For example, the PEG may be PEG 3350 or PEG 4000 as defined in national pharmacopeias. Further examples of suitable PEGs recognized in some national pharmacopeias include Macrogols, for example Macrogol 3350 or Macrogol 4000.

The cleansing solution comprises 10 to 200 g per litre of PEG. Preferably, the solution comprises 10 to 160g per litre of PEG, more preferably 10 to 120 g per litre, for example 20 to 100 g per litre, for example 30 to 90g per litre, for example 40 g per litre or 80 g per litre.

The 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.

The 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 substantially free from sodium bicarbonate.

For example, the 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 2 to 8 g per litre, for example 3 to 7g per litre.

For example, the 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 8 g per litre, for example 1.5 to 6g per litre, for example 2 to 5 g per litre.

In an embodiment, the 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 3 to 7g per litre and potassium chloride may be present at a concentration of 2 to 5 g per litre.

The cleansing solution may comprise 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. In an embodiment, the solution does not comprise a sulphate component.

For example, the solution may comprise a sulphate component at a concentration of 2 to 20 g per litre, for example 5 to 15 g per litre, for example 8 to 15 g per litre, for example 10 to 14 g per litre, for example 12 g per litre. 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.

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.

The 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 and vanilla/lemon and lime e.g. IFF Vanilla and Givaudin Roure Lemon and Lime Flav-o-lok. 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 and grapefruit.

The amount of flavouring required depends on the nature and strength of the flavouring in question. Typically, it is 0.05 to 2.0 g per litre.

The 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). Alternatively, compositions of the invention can be substantially free from added sweeteners, for example to minimize the number of different components in the compositions. Citric acid may also be present as a taste enhancer. Citric acid and/or salts thereof may replace some or all of the ascorbate in solutions of the invention.

The amount of sweetener required depends on the nature and strength of the sweetener being considered. Typically, it is 0.10 to 1.0 g per litre.

The invention thus provides a colon cleansing solution comprising:

a) 60 to 150 g/litre ascorbate component;

b) 10 to 200 g per litre PEG.

c) one or more electrolytes;

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

e) optionally one or more flavouring agents; and

f) optionally one or more sweeteners.

In particular, the invention provides a colon cleansing solution comprising:

a) 60 to 150 g/litre ascorbate component;

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

c) sodium chloride and potassium chloride.

Optional additional ingredients in such a solution include d) sodium sulphate;

e) one or more flavouring agents; and

f) one or more sweeteners.

For example, the solution may consist essentially of water, and:

a) 60 to 150 g/litre ascorbate component;

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

c) sodium chloride and potassium chloride;

d) sodium sulphate;

e) one or more flavouring agents; and

f) one or more sweeteners.

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.

In particular, the invention provides a colon cleansing solution consisting essentially of water and):

a) 60 to 150 g/litre ascorbate component;

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.

In one embodiment, the one or more components of c), d) e) and f) are present in the solution. In an alternative presentation, some or all of components c), d) e) and f) may be provided separately from the solution, for example in a tablet or capsule. 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 and/or d) the one or more alkali metal or alkaline earth metal sulphates, 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.

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.

Preferably, the 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 800 to 1700 mOsmol/kg, for example 900 to 1600 mOsmol/kg, for example 900 to 1300 mOsmol/kg, for example 1000 to 1300 mOsmol/kg.

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.

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. 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.

For a single dose treatment, the solution of the invention may be taken in a volume of 700 to 1500ml. For example, the subject may take from 750ml to 1300ml of the solution, for example 800 to 1200ml, for example 900 to 1100 ml, for example 1000ml. In an embodiment, the subject may take some additional clear fluid. The additional clear fluid may be taken after taking 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 administration of a solution of the invention with clear fluid.

For a split dose treatment, the solution of the invention may be taken with one of the doses having a volume of 200 to 1000ml. For example, the subject may take 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. In an embodiment, the subject may take some additional clear fluid with each or either dose the solution of the invention. 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.

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. The first solution may then 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.

The volume of clear fluid that a subject takes 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 875ml, for example 500ml to 800ml. 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.

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, 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 invention further provides a composition (for example a dry composition, for example a powder) for the preparation of a solution of the invention. A composition can be provided in a quantity for the preparation of a dose of the solution, for example a 500ml dose. The invention provides a composition for admixture with water for the preparation of a colon cleansing solution of the invention, wherein the composition is optionally presented in two or more parts and comprises the following components in the following weight ratios:

a) 0.82 to 10.0 parts ascorbate anion provided by ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and

b) 1.0 part polyethylene glycol.

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.

As set out above, the ascorbate anion may be provided by ascorbic acid, by one or more salts of ascorbic acid, or 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 of the invention.

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.

The weight of the ascorbate component may be 20 to 220g, for example 20 to 150g, for example 20 to 100g, for example 25 to 220g, for example 25 to 150g, for example 25 to 100g, for example 25 to 75g, for example 20 to 60g, for example 50 to 60g.

In an embodiment, the ascorbate component consists essentially of sodium ascorbate alone. For example, it may be present in an amount as mentioned immediately above.

In an alternative embodiment, the ascorbate component comprises (or consists essentially of) sodium ascorbate and ascorbic acid. For example, they may be present in a total amount as mentioned immediately above. They may be in a weight ratio of sodium ascorbate : ascorbic acid from 1:10 to 10:1, for example 2:8 to 8:2, for example 3:7 to 7:3, for example 1.4:1 to 1.8:1.

In an alternative embodiment, the ascorbate component comprises (or consists essentially of) sodium ascorbate and magnesium ascorbate. For example, they may be present in a total amount as mentioned immediately above. They may be in a weight ratio of sodium ascorbate : magnesium ascorbate from 1:10 to 10:1, for example 2:8 to 8:2, for example 3:7 to 7:3, for example 1.8:1 to 1.4:1.

Preferred forms of the PEG are as set out above in relation to solutions of the invention. The composition may comprise 5 to 100 g of PEG. Preferably, the composition comprises 5 to 80g of PEG, more preferably 5 to 60g, for example 10 to 50g, for example 15 to 45g, for example 20 g or 40 g of PEG.

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.

Preferred electrolytes are as set out above in relation to solutions of the invention. For example, the composition may comprise sodium chloride in an amount of 0.5 to 5g, for example 1 to 4 g, for

example 1.5 to 3.5g. For example, the composition may comprise potassium chloride in an amount of 0.5 to 5g, for example 0.5 to 4 g, for example 0.75 to 3g, for example 1.0 to 2.5g.

Preferred alkali metal or alkaline earth metal sulphates are as set out above in relation to solutions of the invention. 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.

Preferred flavouring agents are as set out above in relation to solutions of the invention. For example the amount of flavouring agent may be 0.025 to 1.0 g.

Preferred sweeteners are as set out above in relation to solutions of the invention. For example the amount of sweetener may be 0.05 to 0.5 g.

In particular, the invention provides a composition comprising the following components in the following weight ratios:

a) 0.82 to 10.0 parts ascorbate anion;

b) 1.0 part PEG having an average molecular weight of 3000 to 4000 Da; and

c) sodium chloride and potassium chloride.

Optional components in such a composition include:

d) sodium sulphate;

e) one or more flavouring agents; and

f) one or more sweeteners.

For example, the composition may consist essentially of the following components in the following weight ratios:

a) 0.82 to 10.0 parts ascorbate anion;

b) 1.0 part 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.

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.

In one embodiment, the one or more components of c), d) e) and f) are present in the composition for making up a solution. In an alternative presentation, some or all of components c), d) 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.

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

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.

As mentioned above, 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.

As set out above, the ascorbate anion may be provided by ascorbic acid, by one or more salts of ascorbic acid, or 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 of the invention.

Preferred forms of the PEG are as set out above in relation to solutions of the invention. The composition of the invention preferably comprises ascorbate anion in a weight ratio to PEG of 0.82 to 5.0 :1. More preferably, the weight ratio is 0.9 to 5.0 : 1, for example 1.0 to 4.0 : 1, for example 1.0 to 3.0 : 1, for example 1 to 2 : 1, or 2 to 3 :1.

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;

f) one or more sweeteners.

Preferred electrolytes are as set out above in relation to solutions of the invention. For example, the composition may comprise sodium chloride in a weight ratio to PEG of 0.005 to 1.0 :1, for example 0.01 to 0.6 : 1, for example 0.03 to 0.5 : 1, for example 0.04 to 0.4 : 1, for example 0.05 to 0.3 : 1, for example 0.06 to 0.2 : 1. For example, the composition may comprise potassium chloride in a weight ratio to PEG of 0.005 to 1.0 :1, for example 0.005 to 0.50 : 1, for example 0.01 to 0.50 : 1, for example 0.01 to 0.10 : 1, for example 0.02 to 0.08 : 1, for example 0.03 to 0.07 : 1.

For example, the invention provides a composition comprising the following components in the following weight ratios:

a) ascorbate anion: 0.82 to 10.0 parts;
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 composition is preferably substantially free from sodium bicarbonate. For example, it is substantially free from any bicarbonate.

Preferred alkali metal or alkaline earth metal sulphates are as set out above in relation to solutions of the invention. For example, the composition may comprise a sulphate component (for example sodium sulphate) in a weight ratio to PEG of 0.01 to 0.50 :1, For example, the composition may comprise a sulphate component (for example sodium sulphate) in a weight ratio to PEG of 0.02 to 0.25 : 1, for example 0.03 to 0.22 : 1, for example 0.05 to 0.20 : 1, for example 0.10 to 0.20 : 1.

Preferred flavouring agents are as set out above in relation to solutions of the invention. For example the composition may comprise a flavouring agent in a weight ratio to PEG of 0.0005 to 0.025 : 1, for example 0.001 to 0.025 : 1, for example 0.003 to 0.010 : 1.

Preferred sweeteners are as set out above in relation to solutions of the invention. For example the composition may comprise a sweetener in a weight ratio to PEG of 0.0005 to 0.025 : 1, for example 0.001 to 0.025 : 1, for example 0.002 to 0.010 : 1.

In particular, the invention provides a composition comprising the following components in the following weight ratios:

a) ascorbate anion: 0.82 to 10.0 parts
b) polyethylene glycol having an average molecular weight of 3000 to 4000 Da: 1.0 part; and
c) sodium chloride and potassium chloride.

Optional additional components in such a composition include:
d) sodium sulphate;
e) one or more flavouring agents; and
f) y one or more sweeteners.

Such a composition may consist essentially of the following components in the following weight ratios:

a) ascorbate anion: 0.82 to 10.0 parts

b) polyethylene glycol having an average molecular weight of 3000 to 4000 Da: 1.0 part;

c) sodium chloride and potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

Each of c) and d) may be present in the weight ratios to PEG described above. Each of e) and f) may be as described above and/or be in the weight ratios to PEG described above.

Preferred compositions of the invention are dry compositions, for example dry powder compositions.

As mentioned above, the solutions of the invention find use in cleansing the colon. The invention thus provides, in a second aspect a solution according to the invention for use in cleansing the colon of a mammal.

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.

The solutions and compositions of the invention find particular use in split dose colon cleansing treatments in which the subject takes two different solutions: a first colon cleansing solution, followed by a second colon cleansing solution. Preferably, the solution of the invention is the second colon cleansing solution. Alternatively, it may be the first solution. The invention thus finds utility in a method of cleansing the colon of a mammal comprising:

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

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

the second colon cleansing solution being a solution comprising
a) 60 to 150 g/litre ascorbate; and
b) optionally 10 to 200 g per litre polyethylene glycol.

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

The invention further finds utility in a method of conducting a diagnostic or surgical procedure, for example, a colonoscopy, barium enema examination, sigmoidoscopy or colon surgery, comprising the steps of:

a) cleansing the colon by use of a solution of the invention, and then

b) carrying out the diagnostic or surgical procedure.

The invention provides a kit comprising:
- a first colon cleansing solution, and
- a second colon cleansing solution,
the second colon being a solution according to the invention.

In an embodiment, the first solution is different from the second. The kit may comprise instructions for use.

The invention further provides a first colon solution, and a second colon solution, for use in a method of cleansing the colon comprising:
- the subject taking an effective amount of a first colon cleansing solution;
- the subject taking an effective amount of a second colon cleansing solution,
the second colon cleansing solution being a solution according to the invention.

In an embodiment, the first solution is different from the second.

The second colon cleansing solution is as described hereinabove in relation to solutions and uses of the first aspect of the invention. It is preferably used in a volume as described hereinabove in relation to solutions and uses of the invention.

The first cleansing solution may, for example, be a bowel content suspending agent. The first cleansing solution may comprise polyethylene glycol and/or an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof. The first cleansing solution may be hyper-osmotic.

Preferably, the first colon cleansing solution comprises polyethylene glycol (PEG). The polyethylene glycol (PEG) may have an average molecular weight of 2000 to 8000, for example 2500 to 4500 Da, for example 3000 to 4000 Da. For example, the PEG may be PEG 3350 or PEG 4000 as defined in national pharmacopeias. Further examples of suitable PEGs recognized in some national pharmacopeias include Macrogols, for example Macrogol 3350 or Macrogol 4000.

Preferably, the first colon cleansing solution comprises 70 to 250 g per litre of PEG. Preferably, the solution comprises 130 to 250 g per litre PEG, for example 90 to 200g per litre of PEG, more preferably 100 to 200 g per litre, for example 120 to 150 g per litre, for example 133.3g per litre.

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.

Preferably, the first colon cleansing solution comprises a sulphate component (for example sodium sulphate) at a concentration of 2 to 20 g per litre, for example 2 to 15 g per litre, for example 5 to 15 g per litre, for example 8 to 12 g per litre, for example 8 or 12 g per litre. For example, the first colon cleansing solution comprises 8.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof.

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.

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, 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.

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.

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.

In an embodiment, the first colon cleansing solution may be a solution as commercialised under the tradename MOVIPREP®.

Accordingly, the first colon cleansing solution in a kit of the invention comprises:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 2.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof .

Optional components which may be present in such a first colon cleansing solution in a kit of the invention include:

(iii) one or more electrolytes;

(iv) one or more flavouring agents; and

(v) one or more sweeteners.

Such a first colon cleansing solution in a kit of the invention may consist essentially of water and:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 2.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof ;

(iii) one or more electrolytes;

(iv) one or more flavouring agents; and

(v) one or more sweeteners.

For example, the first colon cleansing solution in a kit of the invention may comprise:

(i) 90 to 200 g per litre PEG having an average molecular weight of 2500 to 4500 Da.

(ii) 2.0 to 15 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof ; and

(iii) 0.5 to 5.0 g per litre sodium chloride, and 0.05 to 5.0 g per litre potassium chloride.

Optional components which may be present in such a first colon cleansing solution in a kit of the invention include:

(iv) one or more flavouring agents; and

(v) one or more sweeteners.

Such a first colon cleansing solution in a kit of the invention may consist essentially of water and:

(i) 90 to 200 g per litre PEG having an average molecular weight of 2500 to 4500 Da.

(ii) 2.0 to 15 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof ;

(iii) 0.5 to 5.0 g per litre sodium chloride, and 0.05 to 5.0 g per litre potassium chloride;

(iv) one or more flavouring agents; and

(v) one or more sweeteners.

The invention further provides, according to a third aspect, a colon cleansing solution comprising:

(i) 130 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 8.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a

mixture thereof.

Optional components which may be present in such a first colon cleansing solution include:

(iii 1) 1.0 to 3.0 g per litre sodium chloride;

(iii 2) 0.5 to 1.5 (for example 0.5 to 1.1) g per litre potassium chloride;

(iv) one or more flavouring agents; and

(v) one or more sweeteners.

Such a first colon cleansing solution may consist of water and:

(i) 130 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 8.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii 1) 1.0 to 3.0 g per litre sodium chloride;

(iii 2) 0.5 to 1.5 (for example 0.5 to 1.1) g per litre potassium chloride;

(iv) one or more flavouring agents; and

(v) one or more sweeteners.

There is also provided a composition for the preparation of such a solution, for example by admixture with water. Preferred amounts of each of components (i) to (v)in the solutions and compositions of the third aspect of the invention are as set out for the first colon cleansing solutions and first colon cleansing compositions hereinabove and hereinbelow.

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. 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.

The first cleansing solution may, for example, have a measured osmolality in the range 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.

A colon cleansing solution according to the third aspect of the invention may be used together with a solution of the first aspect of the invention. Alternatively, it may be used in combination with a different other colon cleansing solution, or used in a suitable volume on its own. If used on its own, it may be used in a single dose or in a split dose administration. The invention provides a method of cleansing the colon of a subject comprising administering a solution of the third aspect of the invention. The solution may be administered on its own or in combination with a further, different, solution.

The invention further provides a kit comprising:

A) a first component, being a composition for the preparation of a first colon cleansing solution as described immediately above by admixture with water; and

B) a second component, being a composition 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 aspect of the invention,

Preferably, the kit further comprises instructions for use.

The invention further provides a kit comprising:
A) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with water; and
B) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with water;
and optional instructions for use,
the second colon cleansing solution being the solution of the invention in water,
the first solution being different from the second.

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.

For example, a kit of the invention may comprise

A) a first component, being a composition for the preparation of a first colon cleansing solution comprising:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da; and
(ii) 2 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

and

B) a second component, being a composition optionally presented in two or more parts for the preparation of a second colon cleansing solution, according to the invention. Optional components which may be present in a first colon cleansing solution in a kit as described above include:

(iii) one or more electrolytes;

(iv) one or more flavouring agents;

(v) one or more sweeteners,

The first colon cleansing solution in a kit as described above may consist essentially of water and:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 2 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii) one or more electrolytes;

(iv) one or more flavouring agents; and

(v) one or more sweeteners,

Preferably, the first solution is of different composition from the second. The concentrations of the components given here are the concentrations attained when the compositions are mixed with water according to the instructions provided with the kit.

The first colon cleansing solution may be used in a volume as described hereinabove, for example 300ml to 1200ml, for example 600ml to 900ml, for example 750ml. The second colon cleansing solution may be used in a volume as described hereinabove, for example 600ml to 900ml, for example 750ml. The second colon cleansing solution may be used in a volume as described hereinabove, for example 250ml up to 1000ml, for example 400ml to 700ml, for example 500ml. Instructions comprised in the kit may instruct the user to prepare a solution by adding water to the required volume, for example a volume as mentioned in this paragraph.

Accordingly, a kit of the invention may comprise:

A) a first component, being a composition for the preparation of a first colon cleansing solution comprising:

(i) 52.5 to 187.5 g PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 1.5 to 15 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof.

and

B) a second component, being a composition optionally presented in two or more parts for the preparation of a second colon cleansing solution, according to the invention,
the first solution being different from the second.

Optional components which may be present in a first component as described above include:

(iii) one or more electrolytes;

(iv) one or more flavourings; and

(v) one or more sweeteners.

For example a kit of the invention may consist essentially of:

A) a first component, being a composition for the preparation of a first colon cleansing solution consisting essentially of:

(i) 52.5 to 187.5 g PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 1.5 to 15 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof.;

(iii) one or more electrolytes;

(iv) one or more flavourings; and

(v) one or more sweeteners;

and

B) a second component, being a composition according to the invention optionally presented in two or more parts for the preparation of a second colon cleansing solution,
the first solution being different from the second.

The first component preferably comprises 97.5 to 187.5 g of PEG, for example 67.5 to 150 g of PEG, more preferably 75 to 150 g, for example 90 to 112.5 g, for example 100 g PEG.

Preferably, the first component comprises a sulphate component (for example sodium sulphate) in an amount of 1.5 to 11.25 g, for example 3.75 to 11.25 g, for example 6 to 9 g, for example 6 or 9 g. For example, the first component comprises 6.0 to 15 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof.

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, 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.

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.

The second component of the kit of compositions of the invention is a composition for the preparation of a solution of the first aspect of the invention as described herein above.

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, the specified volume for the second component may be from 250ml to 1000ml, for example 400ml to 700ml, for example 500ml. Further volumes that may be specified in the instructions are the volumes set out hereinabove in relation to the methods of the invention.

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 time interval (for example the time between an evening and the following morning), by ingestion of the second cleansing solution.

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.

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.

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

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.

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, electrolytes and/or one or more salts of ascorbic acid; and

B2) the third sachet comprises ascorbic acid;

the one or more salts of ascorbic acid in the second sachet (B1) and the ascorbic acid in the third sachet (B2) together providing 60 to 150 g/litre ascorbate component.

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

A) the first sachet comprises:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da.

(ii) 2 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof

(iii) optionally one or more electrolytes;

(iv) optionally one or more flavouring agents; and

(v) optionally one or more sweeteners,

B1) the second sachet comprises:

(i) 10 to 200g per litre polyethylene glycol,

(ii) optionally one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof,

(iii) electrolytes; and

(iv) or one or more salts of ascorbic acid; and

B2) the third sachet comprises ascorbic acid,

the one or more salts of ascorbic acid in the second sachet (B1) and the ascorbic acid in the third sachet (B2) together providing 60 to 150 g/litre ascorbate component.

For example, in a kit of the invention:

A) the first sachet comprises:

(i) 52.5 to 187.5 g PEG having an average molecular weight of 2500 to 4500 Da.

(ii) 1.5 to 15 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof

(iii) optionally one or more electrolytes;

(iv) optionally one or more flavouring agents;

(v) optionally one or more sweeteners,

B1) the second sachet comprises:

(i) 5 to 100g PEG having an average molecular weight of 2500 to 4500 Da,

(ii) optionally one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof,

(iii) electrolytes and/or one or more salts of ascorbic acid; and

B2) the third sachet comprises ascorbic acid,

the one or more salts of ascorbic acid in the second sachet (B1) and the ascorbic acid in the third sachet (B2) together providing 150 to 1000 mmol ascorbate anion.

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.

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.

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

The invention further finds utility in a method of cleansing the colon comprising:
- the subject taking an effective amount of a first colon cleansing solution as described herein;
- the subject taking an effective amount of a second colon cleansing solution as described herein.

In the method, there is typically a time interval between taking the first solution and taking the second solution. 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 cleansing solution and starting to take the second cleansing solution 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 cleansing solutions.

In a fourth aspect, the invention finds utility in a method of cleansing the colon of a subject comprising:

- administering to the subject an effective amount of a first cleansing solution; and then after a time interval

- administering to the subject an effective amount of a second cleansing solution,

wherein the second cleansing solution is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution.

For example, the invention finds utility in a method of cleansing the colon of a subject comprising:

- the subject taking an effective amount of a first cleansing solution; and then after a time interval

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

wherein the second cleansing solution is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid,

or a mixture thereof, in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution.

The amount of solution that constitutes an "effective amount" need not be the same for the first and second solutions.

The method provides satisfactory cleansing of the colon whilst not being wasteful of ascorbic acid component in the first cleansing solution. In addition, the method of the invention provides satisfactory cleansing of the colon with ingestion of a smaller total volume of the solutions than in the prior art. The first cleansing solution is preferably a bowel content suspending agent. The second cleansing solution is a bowel motility agent.

The invention also provides a kit comprising:

- a first colon cleansing solution; and

- a second colon cleansing solution,

wherein the second colon cleansing solution is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first colon cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion in the first colon solution than is present in the second colon cleansing solution.

In some embodiments of the method of the fourth aspect of the invention, the stool output immediately after the ingestion of the first solution may be less copious than after ingestion of the second solution. Given that the subject will often wish to sleep between taking the first bowel cleansing solution and the second solution, it may be advantageous in certain instances for the first cleansing solution to result in a slightly lower stool output than the second cleansing solution.

The invention also provides a kit comprising:

a) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with a clear fluid (for example water); and

b) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with a clear fluid (for example water),

and optionally instructions for use that specify the volume to which each component is to be made up with a clear fluid (for example water),

wherein the second colon cleansing solution, when made up to the instructed specified volume with the clear fluid (for example water), is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first colon cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains, when made up to the instructed specified volume with the clear fluid (for example water), ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion in the first colon solution than in the second colon cleansing solution.

In an embodiment, the invention finds utility in a method of cleansing the colon of a subject comprising:

- administering to the subject an effective amount of a first cleansing solution; and then after a time interval

- administering to the subject an effective amount of a second cleansing solution,

wherein the first cleansing solution contains polyethylene glycol (PEG) and is hyper-osmotic; and wherein the second cleansing solution contains polyethylene glycol (PEG) and is more hyper-osmotic than the first cleansing solution.

For example, the invention finds utility in a method of cleansing the colon of a subject comprising:

- the subject taking an effective amount of a first cleansing solution; and then after a time interval

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

wherein the first cleansing solution contains polyethylene glycol (PEG) and is hyper-osmotic; and wherein the second cleansing solution contains polyethylene glycol (PEG) and is more hyper-osmotic than the first cleansing solution.

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.

The amount of solution that constitutes an "effective amount" need not be the same for the first and second solutions.

The method of the invention provides satisfactory cleansing of the colon with ingestion of a smaller total volume of the solutions than in the prior art. The reduced volume requirement helps to improve patient compliance.

For example, the second cleansing solution may comprise ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof. In solution, ascorbic acid and salts thereof provide ascorbate anion. Depending on the pH of the solution, some ascorbate anion is protonated and thus exists as free ascorbic acid. 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. Ascorbic acid or salts thereof, contribute to the osmotic load, along with other solutes. In one embodiment, the first cleansing solution does not contain ascorbic acid or a salt thereof. Alternatively, the first solution may contain ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof. Typically, if the first solution contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, it contains them in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution.

The invention also provides a kit comprising:

- a first colon cleansing solution; and

- a second colon cleansing solution,

wherein the first cleansing solution contains polyethylene glycol (PEG) and is hyper-osmotic; and wherein the second cleansing solution is a solution according to the invention which contains polyethylene glycol (PEG) and is more hyper-osmotic than the first cleansing solution.

The invention also provides a kit comprising:

a) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with a clear fluid (for example water); and

b) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with a clear fluid (for example water),

and instructions for use that specify the volume to which each component is to be made up with a clear fluid (for example water),

wherein the first cleansing solution contains polyethylene glycol (PEG) and, when made up to the instructed specified volume with the clear fluid (for example water), is hyper-osmotic; and wherein the second cleansing solution contains polyethylene glycol (PEG) and, when made up to the instructed

specified volume with the clear fluid (for example water), is a solution according to the invention which is more hyper-osmotic than the first cleansing solution.

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.

In an embodiment, the invention finds utility in a method of cleansing the colon of a subject comprising:

- administering to the subject an effective amount of a first cleansing solution; and then after a time interval

- administering to the subject an effective amount of a second cleansing solution,

wherein the first cleansing solution and the second cleansing solution are different, and wherein the first cleansing solution contains an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof; and the second cleansing solution is a solution according to the invention.

The amount of solution that constitutes an "effective amount" need not be the same for the first and second solutions.

The first cleansing solution may contain polyethylene glycol (PEG). When made up to the instructed specified volume with water, it is preferably hyper-osmotic. The second cleansing solution contains polyethylene glycol (PEG). When made up to the instructed specified volume with water, it may be hyper-osmotic, preferably more hyper-osmotic than the first cleansing solution.

Typically, if the first solution contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, it contains them in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution. In an embodiment, the first cleansing solution does not contain ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof. Typically, if the second solution contains an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof it contains them in an amount providing a lower concentration of sulphate anion than is present in the first cleansing solution. In an embodiment, the second cleansing solution does not contain an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof.

For example, the invention finds utility in a method of cleansing the colon of a subject comprising:

- the subject taking an effective amount of a first cleansing solution; and then after a time interval

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

wherein the first cleansing solution and the second cleansing solution are different, and wherein the first cleansing solution contains an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof; and the second cleansing solution is a solution according to the invention..

The amount of solution that constitutes an "effective amount" need not be the same for the first and second solutions.

The method described provides satisfactory cleansing of the colon with ingestion of a smaller total volume of the solutions than in the prior art. The reduced volume requirement helps to improve patient compliance.

The second cleansing solution comprises ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof. In solution, ascorbic acid and salts thereof provide ascorbate anion. Ascorbic acid or salts thereof, contribute to the osmotic load, along with other solutes. In one embodiment, the first cleansing solution does not contain ascorbic acid or a salt thereof. Alternatively, the first solution may contain ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof. Typically, if the first solution contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, it contains them in an amount providing a lower concentration of ascorbate anion than is present in the second solution.

The invention also provides a kit comprising:

- a first colon cleansing solution; and

- a second colon cleansing solution,

wherein the first cleansing solution and the second cleansing solution are different, and wherein the first cleansing solution contains an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof; and the second cleansing solution is a solution according to the invention..

The first cleansing solution may contain polyethylene glycol (PEG). When made up to the instructed specified volume with water, it is preferably hyper-osmotic. The second cleansing solution contains polyethylene glycol (PEG). When made up to the instructed specified volume with water, it may be hyper-osmotic, preferably more hyper-osmotic than the first cleansing solution.

The invention also provides a kit comprising:

a) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with a clear fluid (for example water); and

b) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with a clear fluid (for example water),

and instructions for use that specify the volume to which each component is to be made up with a clear fluid (for example water),

wherein the first cleansing solution and the second cleansing solution are different, and wherein the first cleansing solution contains an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof; and the second cleansing solution is a solution according to the invention..

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.

In a further embodiment, the invention finds utility in a method of cleansing the colon of a subject comprising:

- administering to the subject an effective amount of a first cleansing solution; and then after a time interval

- administering to the subject an effective amount of a second cleansing solution,

wherein the first cleansing solution and the second cleansing solution are different and, together, comprise the components:

a) 80 to 250g of a polyethylene glycol;
b) 10 to 150g of ascorbic acid, one or more salts of ascorbic acid or a mixture of ascorbic acid and one or more salts of ascorbic acid (the "ascorbate component");
c) 1 to 15g of an alkali metal or alkaline earth metal sulphate or a mixture of alkali metal or alkaline earth metal sulphates (the "sulphate component");
d) 1 to 15g of electrolytes;
e) optionally one or more sweeteners, and
f) optionally one or more flavourings

wherein the sulphate component is in the first cleansing solution and the ascorbate component is in the second cleansing solution.

The amount of solution that constitutes an "effective amount" need not be the same for the first and second solutions.

The invention further provides a kit comprising two or more compositions for separate admixture with a clear fluid (for example water) wherein the compositions together comprise the components:

a) 80 to 250g of a polyethylene glycol;
b) 10 to 150g of ascorbic acid, one or more salts of ascorbic acid or a mixture of ascorbic acid and one or more salts of ascorbic acid (the "ascorbate component");
c) 1 to 15g of an alkali metal or alkaline earth metal sulphate or a mixture of alkali metal or alkaline earth metal sulphates (the "sulphate component");
d) 1 to 15g of electrolytes;
e) optionally one or more sweeteners;
f) optionally one or more flavourings

wherein the components are arranged such that the sulphate component is in a first dry composition and the ascorbate component is in second dry composition.

For example, the components of the two or more compositions may be in dry powder, granular or other dry form. They may alternatively be in the form of concentrates or slurries. The two or more compositions may be in the same or different physical forms. Components within each of the two or more compositions may be in the same or different physical forms. For example, one or both of the compositions is a dry powder. The clear fluid may be the same or different for the two or more compositions.

The invention further provides a kit comprising two or more solutions wherein the solutions together comprise the components:

a) 80 to 250g of a polyethylene glycol;
b) 10 to 150g of ascorbic acid, one or more salts of ascorbic acid or a mixture of ascorbic acid and one or more salts of ascorbic acid (the "ascorbate component");
c) 1 to 15g of an alkali metal or alkaline earth metal sulphate or a mixture of alkali metal or alkaline earth metal sulphates (the "sulphate component");
d) 1 to 15g of electrolytes;
e) optionally one or more sweeteners;

f) optionally one or more flavourings

wherein the components are arranged such that the sulphate component is in a first solution and the ascorbate component is in second solution.

For example, each of the first and second compositions (or solutions) may contain some of the electrolytes of component d). For example, each of the first and second compositions (or solutions) may contain some of the polyethylene glycol of component a). Alternatively, the polyethylene glycol of component a) may be contained only in the first composition (or solution). For example, each of the first and second compositions (or solutions) may contain some of the sweetener of component e). For example, each of the first and second compositions (or solutions) may contain some of the flavouring of component f). The first composition (or solution) may contain more of component e) or f) than the second composition (or solution).

In an alternative embodiment, a method, solution or kit is provided wherein the first cleansing solution and the second cleansing solution have different compositions and, together, comprise the components:

a) 80 to 250g of a polyethylene glycol;
b) 10 to 150g of ascorbic acid, one or more salts of ascorbic acid or a mixture of ascorbic acid and one or more salts of ascorbic acid (the "ascorbate component");
c) 1 to 15g of an alkali metal or alkaline earth metal sulphate or a mixture of alkali metal or alkaline earth metal sulphates (the "sulphate component");
d) 1 to 15g of electrolytes;
e) optionally one or more sweeteners, and
f) optionally one or more flavourings;

wherein the pair of solutions is not a combination in which :

the first solution contains 100g PEG3350, 3g $Na_2SO_4$, 1.4g NaCl and 0.3g KCl; or the first solution contains 100g PEG3350, 6g $Na_2SO_4$, 1.6g NaCl and 0.7g KCl; or the first solution contains 100g PEG3350, 9g $Na_2SO_4$, 2.0g NaCl and 1.0g KCl; and

the second solution contains 40g PEG3350, 3.5g NaCl, 2.2g KCl and 56.6g sodium ascorbate; or the second solution contains 20g PEG3350, 2.7g NaCl, 1.3g KCl, 33.9g sodium ascorbate and 20.1g ascorbic acid; or the second solution contains 40g PEG3350, 2.8g NaCl, 3.1g KCl 33.9g sodium ascorbate and 20.1g ascorbic acid; or the second solution contains 40g PEG3350, 6g $Na_2SO_4$, 2.8g NaCl, 2.0g KCl and 33.9g sodium ascorbate; or the second solution contains 40g PEG3350, 3.1g NaCl, 1.3g KCl, 33.9g sodium ascorbate and 21.4g magnesium ascorbate.

The combined volume of the first and second cleansing solutions 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 1250ml. For example the first cleansing solution may have a volume of 750ml and the second cleansing solution may have a volume of 500ml.

In an embodiment, the subject may take some additional clear fluid after taking the first cleansing solution but before taking the second cleansing solution; and/or after taking the second cleansing solution. In an embodiment, the total amount of additional clear fluid that the subject takes is in the range 1000ml to 2500ml, for example 1750ml.

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, 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 time interval in the method of the invention is generally 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 cleansing solution and starting to take the second cleansing solutions 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 cleansing solutions. The time between finishing taking the first solution and starting to take the second solution is somewhat less, and that depends on the time the subject takes to complete the first solution. Typically, the first solution is taken over a period of up to two hours, for example an hour. Therefore the time between finishing taking the first solution and starting to take the second solution is for example 11 to 15 hours, for example 13 hours.

During the time interval between the administration of the first cleansing solution and the second cleansing solution, 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 or senna. Examples of stimulant laxatives also include additional osmotic agents for example magnesium salts, for example magnesium citrate. If a stimulant laxatives is included in the regimen, the length of the time interval can be shortened. For example, it may be 1 to 15 hours, for example 1 to 12 hours, for example 2 to 10 hours.

During the time interval between the administration of the first cleansing solution and the second cleansing solution, 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 cleansing solution.

The second cleansing solution, and optionally the first cleansing solution contains ascorbic acid, one or more salts thereof, or a mixture thereof. For convenience, they will be referred to herein as the "ascorbate component".

Suitable salts of the ascorbic acid include alkali metal and alkaline earth metal salts. For example, preferred salts of ascorbic acid include sodium ascorbate and magnesium ascorbate. In an embodiment, one of sodium ascorbate and magnesium ascorbate is present.

In one embodiment, the ascorbate component comprises both ascorbic acid and one or more salts of ascorbic acid. For example, the ascorbate component may comprise ascorbic acid and sodium ascorbate. For example, the ascorbate component may comprise ascorbic acid and magnesium ascorbate.

In an embodiment, a mixture of salts of ascorbic acid is used. For example, both sodium ascorbate and magnesium ascorbate may be present. They may be present with ascorbic acid, or without ascorbic acid.

The second cleansing solution contains a higher concentration of ascorbate anion than is present in the first cleansing solution. For example, the second cleansing solution contains twice the concentration of the ascorbate anion than the first cleansing solution or more. For example, the second solution contains three times or more, four times or more, or five times or more the concentration of the ascorbate anion than the first cleansing solution. For example, the second cleansing solution contains a concentration of the ascorbate anion that is at least 50mmol per litre greater than that of the first cleansing solution. That is to say that the second solution contains a concentration of ascorbate anion that is at least 50mmol per litre greater than that of the first solution. For example, the second

solution contains a concentration of the ascorbate anion that is greater by at least 100mmol per litre, for example at least 200mmol per litre, at least 300mmol per litre.

For example, the first cleansing solution may be substantially free from an ascorbate component.

For example, the second cleansing solution may comprise:

- 56.6g sodium ascorbate, or
- 33.9g sodium ascorbate and 20.1g ascorbic acid, or
- 33.9g sodium ascorbate, or
- 33.9g sodium ascorbate and 21.4 g magnesium ascorbate.

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

For example, the second cleansing solution may comprise 20g or 40g PEG 3350. For example, the second cleansing solution may have a volume of 500ml.

The first cleansing solution may comprise polyethylene glycol and/or an alkali metal sulphate, an alkaline earth metal sulphate, or a mixture thereof.

The polyethylene glycol (PEG) in the first cleansing solution may be as described immediately above for the second cleansing solution. The PEG in the first cleansing solution can be a different PEG from the PEG in the second cleansing solution. For example, one PEG may be PEG3350 and the other PEG may be PEG4000. For example, the first cleansing solution may comprise 100g PEG 3350. For example, the first cleansing solution may have a volume of 750ml.

The first cleansing solution preferably comprises an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof. 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 alkali metal sulphate, an alkaline earth metal sulphate or the mixture thereof is or includes sodium sulphate. Preferably, an alkali metal sulphate or alkaline earth metal sulphate (for example sodium sulphate) is anhydrous.

For example, the first cleansing solution may have a volume of 750ml and comprise 3g, 6g or 9g of sodium sulphate.

The first and/or second cleansing solution(s) may further comprise one or more of:

a) one or more electrolytes;
b) one or more flavouring agents;
c) one or more sweeteners.

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 first and/or second solution is substantially free from sodium bicarbonate.

For example, the first cleansing solution may have a volume of 750ml and comprise 1.4g sodium chloride and 0.3g potassium chloride; or 1.6g sodium chloride and 0.7g potassium chloride; or 2.0g sodium chloride and 1.0g potassium chloride.

For example, the second cleansing solution may have a volume of 500ml and comprise 3.5g sodium chloride and 2.2g potassium chloride; or 2.7g sodium chloride and 1.3g potassium chloride; or 2.8g sodium chloride and 1.3g potassium chloride; or 2.8g sodium chloride and 2.0g potassium chloride; or 3.1g sodium chloride and 1.3g potassium chloride. For example the second cleansing solution is substantially free from sodium bicarbonate.

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.

The first and/or second cleansing solution(s) preferably include a flavouring agent. 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. 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 and vanilla/lemon and lime e.g. IFF Vanilla and Givaudin Roure Lemon and Lime Flav-o-lok. 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 and orange. The most preferred flavourings are lemon flavour and orange flavour.

The first and/or second cleansing solution(s) preferably include 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). Alternatively, compositions of the invention can be substantially free from added sweeteners, for example to minimize the number of different components in the compositions. Citric acid may also be present as a taste enhancer.

As mentioned above, in the various embodiments of the fourth aspect of the invention, the first or second solution may include electrolytes. In an alternative embodiment, some or all of the electrolytes may be provided in a tablet or capsule for co-administration with the respective solution. A tablet or capsule may include sweetener or flavouring.

The first cleansing solution may, for example, have a measured osmolality in the range 200 to 1500 mOsmol/kg. In a preferred embodiment, it 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 320 to 1500 mOsmol/kg. 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.

The second 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 800 to 1700 mOsmol/kg, for example 900 to 1600 mOsmol/kg, for example 900 to 1300 mOsmol/kg, for example 1000 to 1300 mOsmol/kg.

In an embodiment, the second cleansing solution is more hyper-osmotic than the first cleansing solution. For example, the ratio between the osmolality of the second cleansing solution and the osmolality of the first cleansing solution is from 6:1 to 1.3:1. For example, the ratio is from 5:1 to 1.3:1, for example from 3.5:1 to 1.5:1, for example from 2.5:1 to 1.6:1.

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.

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.

The method described 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, barium enema examination, sigmoidoscopy (for example flexible sigmoidoscopy) or colon surgery. The method 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.

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

The invention further provides a kit comprising:

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

wherein the second colon cleansing solution is according to the invention and is hyper-osmotic; and wherein the first colon cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion in the first colon solution than is present in the second colon cleansing solution.

A kit may further comprise instructions for use. The use may be as described above in relation to methods.

In a kit of the invention, the components of the first and second solutions are as described hereinabove in relation to methods.

The invention further provides a first solution, and a second solution, for use in a method of cleansing the colon of a subject comprising:

- the subject taking an effective amount of a first cleansing solution; and then after a time interval

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

wherein the second cleansing solution is according to the invention and is hyper-osmotic; and wherein the first cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution.

The invention further provides a solution that is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, for use in a method of cleansing the colon of a subject comprising:

- the subject taking an effective amount of a first cleansing solution; and then after a time interval

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

wherein the second cleansing solution is according to the invention and is hyper-osmotic; and wherein the first cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution.

In an embodiment, the first cleansing solution is substantially free from ascorbic acid and salts thereof.

In an embodiment, the invention provides a kit comprising:

a) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with a clear fluid (for example water); and

b) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with a clear fluid (for example water),

and instructions for use that specify the volume to which each component is to be made up with water,

wherein the second colon cleansing solution, when made up to the instructed specified volume with the clear fluid (for example water), is a solution according to the invention and is hyper-osmotic; and wherein the first colon cleansing solution is either

substantially free from ascorbic acid and salts thereof, or contains, when made up to the instructed specified volume with the clear fluid (for example water), ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion in the first colon solution than in the second colon cleansing solution.

The constituent parts of the composition for the preparation of a first cleansing solution by admixture with water are, for example, as described hereinabove in relation to the first solution. The constituent parts of the composition for the preparation of a second cleansing solution by admixture with water are, for example, as described hereinabove in relation to the second solution.

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.

In an embodiment, a kit of the invention has instructions in which the specified volume of water for each solution is less than one litre. For example, the combination of the specified volumes of the first and second cleansing solutions 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 1250ml. For example a volume of 750ml may be specified for the first cleansing solution and a volume of 500ml may be specified for the second cleansing solution. The instructions may specify that a cleansing solution is consumed immediately after it has been prepared. They may specify that the cleansing solution is prepared and then stored in a fridge before consumption at a slightly later time.

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.

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 be 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.

If a flavouring component and/or sweetening component is present in the first or second solution, then in a kit of the invention, the flavouring and/or sweetener component for the relevant solution may be provided in a separate container from the other constituents of that solution. Alternatively, the flavouring and/or sweetener may be in the same container as one or more other components. For example, any flavouring or sweetener may be in the same container as PEG.

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

In one embodiment, a kit comprises:

a) a first sachet comprising a first composition for the preparation of a first cleansing solution;
b) a second sachet;
c) a third sachet;
and instructions for use

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

wherein the first and second cleansing solutions are as described herein-above.

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

a) the first sachet comprises polyethylene glycol and/or sodium sulphate, optional flavouring and/or optional sweetener;
b) the second sachet comprises polyethylene glycol, and optionally further components including one or more selected from an alkali metal sulphate, an alkaline earth metal sulphate, or a mixture thereof, electrolytes, one or more salts of ascorbic acid, flavouring and sweetener; and
c) the third sachet comprises ascorbic acid and optionally one or more salts of ascorbic acid.

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 and one dose of the second 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.

For example, in a kit of the invention:

a) the first sachet comprises 100g PEG 3350, 3g sodium sulphate, 1.4g sodium chloride and 0.3g potassium chloride; or 100g PEG 3350, 6g sodium sulphate, 1.6g sodium chloride and 0.7g potassium chloride; or 100g PEG 3350, 9g sodium sulphate, 2.0g sodium chloride and 1.0g potassium chloride; and optional flavouring and/or optional sweetener;

b) the second sachet comprises (i) 40g PEG 3350, 3.5g sodium chloride and 2.2g potassium chloride; or (ii) 20g PEG 3350 2.7g sodium chloride and 1.3g potassium chloride; or (iii) 40g PEG 3350, 2.8g sodium chloride and 1.3g potassium chloride; or (iv) 40g PEG 3350, 2.8g sodium chloride and 2.0g potassium chloride; or (v) 40g PEG 3350, 3.1g sodium chloride and 1.3g potassium chloride; and optional flavouring and/or optional sweetener; and

c) the third sachet comprises for use with the respectively numbered second sachet (i) 56.6g sodium ascorbate; or (ii) and (iii) 33.9g sodium ascorbate and 20.1g ascorbic acid; or (iv) 33.9g sodium ascorbate; or (v) 33.9g sodium ascorbate and 21.4g magnesium ascorbate.

In such kits, the contents of the sachets may consist essentially of the recited components.

As mentioned above, some or all of the electrolytes may be provided in a tablet or capsule for co-administration with the respective solution. Accordingly, in a kit as described immediately above, some or all of the sodium chloride and potassium chloride in the first or second sachet may instead be provided in a tablet or capsule.

In an embodiment, the kit 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.

Unless stated otherwise, a composition that is described herein as comprising a recited set of components is to be taken as comprising the components in admixture. If a composition is said to be presented in two or more parts, then the components need not all be in physical admixture. Typically, they are provided together in the article provided to the subject.

To summarise, the invention provides a colon cleansing solution comprising:
a) 60 to 150 g/litre ascorbate component (provided by ascorbic acid, one or more salts of ascorbic acid selected from sodium ascorbate, potassium ascorbate, magnesium ascorbate and calcium ascorbate, or a mixture thereof);; and
b) 10 to 200 g per litre PEG having an average molecular weight of 3000 to 4000 Da; preferably 20 to 100g per litre.

Optional components in such a solution include:
c) sodium chloride (for example 3 to 7g per litre) and potassium chloride (for example 2 to

5g per litre);

d) sodium sulphate (if present, for example 2 to 20g per litre);

e) one or more flavouring agents; and

f) one or more sweeteners.

Preferably such a solution consists essentially of water and:

a) 60 to 150 g/litre ascorbate component (provided by ascorbic acid, one or more salts of ascorbic acid selected from sodium ascorbate, potassium ascorbate, magnesium ascorbate and calcium ascorbate, or a mixture thereof);

b) 10 to 200 g per litre PEG having an average molecular weight of 3000 to 4000 Da; preferably 20 to 100g per litre;

c) sodium chloride (for example 3 to 7g per litre) and potassium chloride (for example 2 to 5g per litre);

e) one or more flavouring agents; and

f) one or more sweeteners.

The invention also provides a composition (optionally presented in two or more parts) for admixture with water to provide a solution of the invention. The electrolytes may optionally be provided as a tablet or a capsule to be co-administered with the solution.

The invention also finds utility in a method of cleansing the colon of a subject comprising:

- administering to the subject an effective amount of a first cleansing solution; and then after a time interval

- administering to the subject an effective amount of a second cleansing solution,

wherein the second cleansing solution is according to the invention and is hyper-osmotic, containing ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof (for example ascorbic acid and sodium ascorbate, for example sodium ascorbate); and wherein the first cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution. The second cleansing solution may comprises PEG and may comprise electrolytes (for example sodium chloride and potassium chloride). The first solution may comprise PEG; it may comprise an alkali metal or alkaline earth metal sulphate (for example sodium sulphate); it may comprise electrolytes (for example sodium chloride and potassium chloride). There are also provided kits comprising a first and a second solution according to the invention, and kits comprising compositions for preparing the first and second solutions.

**Experimental**

**Pharmacokinetic evaluation and mass balance study**

An investigation into the pharmacokinetics and mass balance of a solution in water of MOVIPREP powder for oral solution was carried out following oral administration using single dose or split dose intake in healthy male subjects.

Subjects:
The subjects were healthy male volunteers aged 18 to 45 years. The subjects' written informed consent was obtained. The subjects were willing, able and competent to complete the procedure and to comply with the study instructions. The subjects had to not meet any of the exclusion criteria. 24 subjects were randomly allocated into two groups: 12 into the single-dose group and 12 into the split-dose group.

Study medication:
The study medication administered was a solution in water of MOVIPREP powder for oral solution. The total dose was 2 litres of the solution for each subject. The solution contains, per litre:

PEG3350: 100g
Sodium Sulphate: 7.500g
Ascorbic Acid: 4.700g
Sodium Ascorbate: 5.900g
Sodium chloride: 2.691g
Potassium chloride: 1.015g
Lemon-flavour and Sweetener

The 4.700g ascorbic acid and 5.900g sodium ascorbate together provide the equivalent of 9.944g ascorbic acid. A 2 litre dose thus provides the equivalent of 19.89g of ascorbic acid.

Treatment Regimens:
The single dose group took the solution as follows:
2L of solution were consumed between 17:00 and 20:00 on Day -1. The first litre was consumed within the first hour, with at least 500ml of additional clear fluid. The second litre was consumed within two hours, with at least 500ml of additional clear fluid.

The split dose group took the solution as follows:
1L of solution was consumed between 18:00 and 19:30 on Day -1. The litre was consumed within the 90 minutes, with at least 500ml of additional clear fluid. The second litre was consumed between 07:00 and 08:30 on Day 0 (the day on which a colonoscopy procedure would be carried out in a

clinical situation). The litre was consumed within the 90 minutes, with at least 500ml of additional clear fluid.

Sample collection for monitoring of PK parameters in blood and recovery of components in faeces and urine:
Urine and faeces were collected throughout the procedure. Cumulative content amounts of components under investigation in the urine were obtained from measured concentrations of the components and measured actual volume of urine. Similarly, the cumulative content amounts of components under investigation in the faeces were obtained from measured concentrations of the components and measured actual mass of faeces. The defined time points for analysis of urine and faeces were at 0hr, 2hr, 4hr, 8hr, 12hr, 12.97hr, 18hr, 24hr, 25.93hr, 36hr, 48hr, 60hr, 72hr and 120hr after the start of intake of the first litre of study medication. Blood samples were collected from the subjects at particular time points through the procedure.

Sample evaluation:
The cumulative amounts of ascorbic acid, PEG3350, chloride, sulphate, sodium and potassium in plasma, faeces and urine were evaluated. The PK profiles of ascorbic acid, PEG3350, chloride, sulphate, sodium and potassium in the plasma were evaluated. Plasma renin and aldosterone were checked at all PK time points.

For higher accuracy, the analysis of the recovery of ascorbic acid was extended to include also its metabolites dehydro-ascorbic acid and oxalic acid in urine and faeces.

Completion of study:
Of the 12 subjects in the single-dose group, 4 had to be excluded from the analysis due to protocol violations, so 8 subjects were evaluated.

Of the 12 subjects in the split-dose group, 1 had to be excluded from the analysis due to protocol violations, so 11 subjects were evaluated.

Results:

General:
The mean cumulative recovery of ascorbic acid (including metabolites dehydroascorbic acid and oxalic acid) and PEG3350 in faeces and urine was comparable for the subjects in both treatment groups. The data collected on the cumulative amount of chloride, sulphate, sodium and potassium were comparable between the subjects in both treatment groups insofar as there was a continuous elimination in urine plus faeces (i.e. no plateau was reached). Furthermore, the PK parameters ($AUC_{0\rightarrow\infty}$, $AUC_{last}$, $C_{max}$, $K_{el}$, $V_d$ and $t_{1/2}$) determined for ascorbic acid, sulphate, chloride, sulphate,

sodium and potassium were comparable for the subjects in the single dose and the split dose group; especially the values for $AUC_{last}$ (i.e. exposure) were nearly identical for both groups.

Recovery and mass balance of ascorbic acid:

The ascorbic acid was to a significant extent excreted in faeces. The cumulative recovery of ascorbic acid and its metabolites from 0 to 120 hours after the start of intake of the first litre of study medication is shown in Table 1 for the single-does group and in Table 2 for the split-dose group. In the final column of Tables 1 and 2, there is given the plasma concentration of ascorbate (not including its metabolites) at the stated time points. That information in Tables 1 and 2 is taken from the graphs shown in Figures 1 and 2 respectively.

Table 1: Single Dose Group

| **Time / hr** | **Urine / g** | **Faeces / g** | **Total / g** | **Plasma µg/ml** |
|---|---|---|---|---|
| **0** | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.00 ± 0.000 | 11.5 |
| **2** | 0.125 ± 0.0964 | 4.718 ± 3.5639 | 4.84 ± 3.643 | 43.0 |
| **4** | 0.456 ± 0.1193 | 11.961 ± 1.4291 | 12.42 ± 1.418 | 52.5 |
| **8** | 1.278 ± 0.2492 | 13.577 ± 1.2776 | 14.86 ± 1.243 | 38.0 |
| **12** | 1.472 ± 0.3116 | 13.587 ± 1.2882 | 15.06 ± 1.248 | 23.0 |
| **12.97** | 1.472 ± 0.3116 | 13.587 ± 1.2882 | 15.06 ± 1.248 | 20.0 |
| **18** | 2.202 ± 0.4252 | 13.909 ± 1.2864 | 16.11 ± 1.253 | 17.2 |
| **24** | 2.740 ± 0.5025 | 13.947 ± 1.2870 | 16.69 ± 1.210 | 13.2 |
| **25.93** | 2.814 ± 0.5112 | 13.952 ± 1.2859 | 16.77 ± 1.218 | 13.2 |
| **36** | 3.162 ± 0.6042 | 13.952 ± 1.2860 | 17.11 ± 1.209 | 12.8 |
| **48** | 3.977 ± 0.7192 | 13.972 ± 1.2901 | 17.95 ± 1.369 | 12.3 |
| **60** | 4.605 ± 0.9177 | 13.982 ± 1.2964 | 18.59 ± 1.733 | 12.0 |
| **72** | 5.104 ± 1.1514 | 14.018 ± 1.3020 | 19.12 ± 1.920 | 12.3 |
| **120** | 6.501 ± 1.9053 | 14.041 ± 1.3203 | 20.54 ± 2.723 | Not measured |
| | | | | |
| **From 12.97 to 25.93** | 1.342 ± 0.4857 | 0.365 ± 0.4459 | 1.707 ± 0.780 | N/A |

Table 2: Split Dose Group

| **Time / hr** | **Urine / g** | **Faeces / g** | **Total / g** | **Blood µg/ml** |
|---|---|---|---|---|
| **0** | 0.000 ± 0.000 | 0.000 ± 0.000 | 0.00 ± 0.000 | 10.5 |
| **2** | 0.248 ± 0.3552 | 2.356 ± 2.0088 | 2.60 ± 2.213 | 36.5 |
| **4** | 0.586 ± 0.3951 | 3.810 ± 2.4661 | 4.40 ± 2.592 | 34.3 |
| **8** | 0.860 ± 0.5437 | 4.836 ± 2.4106 | 5.70 ± 2.607 | 25.0 |
| **12** | 0.860 ± 0.5437 | 4.836 ± 2.4106 | 5.70 ± 2.607 | 16.2 |
| **12.97** | 1.180 ± 0.6712 | 5.022 ± 2.4831 | 6.20 ± 2.772 | 15.0 |
| **18** | 2.220 ± 0.7555 | 10.239 ± 4.6259 | 12.46 ± 4.885 | 25.5 |
| **24** | 3.323 ± 1.3183 | 11.010 ± 4.5147 | 14.33 ± 4.993 | 16.0 |

| | | | | |
|---|---|---|---|---|
| **25.93** | 3.482 ± 1.3946 | 11.047 ± 4.5342 | 14.53 ± 5.123 | 15.8 |
| **36** | 4.351 ± 2.3023 | 11.062 ± 4.5147 | 15.41 ± 5.556 | 13.0 |
| **48** | 5.432 ± 3.3304 | 11.104 ± 4.5497 | 16.54 ± 6.200 | 11.6 |
| **60** | 6.228 ± 3.9837 | 11.109 ± 4.5519 | 17.34 ± 6.685 | 11.4 |
| **72** | 7.069 ± 4.5654 | 11.141 ± 4.5649 | 18.21 ± 7.104 | 11.4 |
| **120** | 9.123 ± 5.4605 | 11.195 ± 4.6225 | 20.32 ± 7.930 | Not measured |
| | | | | |
| **From 12.97 to 25.93** | 2.302 ± 1.2932 | 6.025 ± 2.4704 | 8.327 ± 3.113 | N/A |

Discussion:

Of the 19.89 g ingested ascorbic acid equivalents contained in 2 litres of MOVIPREP solution 103.35% were found to be recovered in urine and faeces of the single-dose group subjects after 120 hours, and 103.05% were found to be recovered in urine and faeces of the subjects in the split-dose group after 120 hours. There was no statistically significant difference between the total recovered amount of ascorbic acid between the two groups.

There was, however, a difference between the timing of the recovery and between the distribution of the ascorbic acid between urine and faeces. It is seen in Tables 1 and 2 that in the split dose group, the distribution of the total recovered 20.32g ascorbic acid between urine and faeces is in the ratio 9.123g : 11.195g, ie 44.9% : 55.1% (or 1:1.23) whilst, in the single dose group, the distribution of the total recovered 20.54g ascorbic acid between urine and faeces is in the ratio 6.501g : 14.041g, ie 31.6% : 68.4% (or 1:2.16).

The final column of each of Tables 1 and 2 shows the plasma level of ascorbate/ascorbic acid at the stated time points. The measurement does not include metabolites of ascorbic acid, and it does not take account of ascorbate in other compartments in the body. Nevertheless, increases in plasma ascorbate are clearly seen in the hours following administration of the solution.

In order to compare the recovery of ascorbic acid during the different phases of the protocol, two time intervals were defined: the first time interval was between time zero, i.e. the start of the intake of the first litre of study medication and time "x", where "x" represents the minimal starting time point of the intake of the second litre of study medication for split dose group (from time 0 to 12.97 hrs). The second time interval was from time "x" to time 2x (from 12.97 to 25.93 hrs).

It is seen that, during the second time interval, 6.025g of ascorbic acid are recovered from faeces of the split-dose group, compared with 5.022g during the first time interval. The 6.025g in the second time interval is closer to being half of the 13.587g seen over the first time interval in the single-dose group. That is to say that the second dose of the split-dose treatment follows a similar time course to the (only) dose in the single-dose treatment.

The differences in the recovered amounts of components between the first and the second time intervals are statistically significant for ascorbic acid (incl metabolites) in faeces (p=0.0078) and urine plus faeces (p=0.0078) for the single dose group subjects, and in urine (p=0.0020) and urine plus faeces (p=0.0322) of the split dose group subjects.

## Examples

### 1. Bowel Cleansing Solutions

Example 1a – Contents of solutions:

The following bowel cleansing solutions of the invention were prepared. For solution A1, the components shown in Table 3 were combined in dry powder form and sealed in a sachet. The solution was then prepared by dissolving the contents in water to the volume stated in the penultimate column. Solutions A2 and A3 were prepared in an analogous manner.

**Table 3**

| Sol'n | PEG3350 /g | $Na_2SO_4$ (anhyd)/g | NaCl /g | KCl /g | Water to Vol /ml | V(350) / ml |
|---|---|---|---|---|---|---|
| **A1** | 100 | 3 | 1.4 | 0.3 | 750 | 725 |
| **A2** | 100 | 6 | 1.6 | 0.7 | 750 | 915 |
| **A3** | 100 | 9 | 2.0 | 1.0 | 750 | 1080 |

For solution B1, the components shown in Table 4 were combined in dry powder form and sealed in respective sachets A and B as indicated in the table. The solution was then prepared by mixing the contents of the two sachets together and then dissolving them in water to the volume stated in the penultimate column. Solutions B2 to B5 were prepared in an analogous manner.

**Table 4**

| Sol'n | Sachet A | | | | Sachet B | | | Water to Vol /ml | V(350) / ml |
|---|---|---|---|---|---|---|---|---|---|
| | PEG3350 /g | $Na_2SO_4$ (anhyd)/g | NaCl /g | KCl /g | Sodium Ascorbate / g | Ascorbic Acid / g | Magnesium Ascorbate / g | | |
| **B1** | 40 | - | 3.5 | 2.2 | 56.6 | - | - | 500 | 2000 |
| **B2** | 20 | - | 2.7 | 1.3 | 33.9 | 20.1 | - | 500 | 1570 |
| **B3** | 40 | - | 2.8 | 1.3 | 33.9 | 20.1 | - | 500 | 1600 |
| **B4** | 40 | 6 | 2.8 | 2.0 | 33.9 | - | - | 500 | 1700 |
| **B5** | 40 | - | 3.1 | 1.3 | 33.9 | - | 21.4 | 500 | 1700 |

The solutions additionally contained sweetener and flavouring sufficient to improve their palatability.

In the case of the solutions in Table 4, those components were in sachet A. The solutions were not optimised for palatability.

Example 1b – V(350) Osmolality measurements:
In order to assess the osmotic strength of the solutions, it was determined how much water was required to provide a solution with measured osmolality of 350mOsmol/kg from the amounts of the components in Tables 3 and 4.

To each solution prepared by dissolving the components in Tables 3 and 4 above in 500ml of deionised was added further deionised water until it reached an osmolality of 350mOsmol/kg. After a volume was found in a first experiment, a second experiment was carried out in which the volume of water found in the first experiment was added to the contents of a new sachet in one aliquot. It was then checked that the resulting solution had an osmolality of 350 +/- 7 mOsmol/kg. In every case, it did. The volumes are recorded in Tables 3 and 4 in the final columns. Osmolalities were measured using an Advanced Instruments, Inc Model 3250 osmometer. The osmometer was operated following standard instructions: after the device passes a calibration check, the "Low Range" osmolality range (0 to 2000 mOsmol/kg) is selected, and a sample tube containing 250µl of sample solution is placed in the freezing chamber. The "start" button is then pressed. When the measurement is completed, the device displays the measurement result and that is recorded.

**Example 2: Bowel cleansing of subjects**

An open, randomised, single centre phase I study to investigate the pharmacodynamic effects (stool weight) of the various modified gut cleansing solutions. The study had two sequential parts (Part 1 and Part 2). In both parts investigational medicinal product (IMP) was administered in the evening of Day 1 and the morning of Day 2. In Part 1 of the study, three different solutions A given in the evening were combined in turn with a fixed solution B given in the morning. In addition, one group of subjects received MOVIPREP®, as reference product.

In Part 2 of the study, the selected solution A from Part 1 was given as the evening dose in combination with four different solutions B as the morning dose. Stool output was assessed.

**Number of patients (planned and analysed):**
Planned: at least 160 evaluable cases in the entire study (20 evaluable subjects per treatment group)

Analysed: 161 evaluable cases (part A: 81 subjects; part B: 80 subjects). Patients were subjected to inclusion and exclusion criteria.

**Dosage regimen:**

Each subject received his/her solution regimen in the split dose intake:

- Evening dose: Day 1; start intake between 17:00 and 18:00 pm for an intake period of up to 2 hours after fasting from 14:00 pm.
- Morning dose: Day 2; start intake between 7:00 and 8:00 am for an intake period of up to 2 hours. 4 hours after complete intake of the morning dose, the first meal was provided, but not before completion of the planned safety laboratory blood drawing.

After the end of the intake of each dose of the investigational solution, the subjects were instructed to take further clear liquid (water).

Screened healthy subjects provided one stool collection after a complete bowel motion in the 7 days before the planned admission to the unit for baseline evaluation. After admission to the unit, all defecated faeces were collected after each bowel movement. Stool appearance and weight was determined for each collected stool fraction. Faecal samples were taken until at least 15:00 pm on Day 4 and an attempt was made to collect a final faecal sample prior to discharge from the phase I unit.

**Solutions: Part 1:**

**Table 5a**

| Sol'n | PEG3350 /g | $Na_2SO_4$ (anhyd)/g | NaCl /g | KCl /g | Ascorbic acid | Sodium ascorbate | Water to Vol /ml |
|---|---|---|---|---|---|---|---|
| A2 | 100 | 6 | 1.6 | 0.7 | - | - | 750 |
| A3 | 100 | 9 | 2.0 | 1.0 | - | - | 750 |
| A4 | 75 | 5.6 | 2.0 | 0.8 | - | - | 750 |
| A-Mov | 100 | 7.5 | 2.691 | 1.015 | 4.7 | 5.9 | 1000 |

**Table 5b**

| Sol'n | Sachet A | | | | Sachet B | | | Water to Vol /ml |
|---|---|---|---|---|---|---|---|---|
| | PEG3350 /g | $Na_2SO_4$ (anhyd)/g | NaCl /g | KCl /g | Sodium Ascorbate / g | Ascorbic Acid / g | Magnesium Ascorbate / g | |
| B3 | 40 | - | 2.8 | 1.3 | 33.9 | 20.1 | - | 500 |
| B-Mov | 100 | 7.5 | 2.691 | 1.015 | 5.9 | 4.7 | | 1000 |

The subjects were randomised into four groups (1:1:1:1), and given one of the three solutions A2, A3 and A4 in Table 5a as the evening dose, followed by solution B3 as the morning dose, or (for the fourth group) given MOVIPREP solution for both doses (ie A-Mov followed by B-Mov). Solutions

A2 and A3 are solutions of the invention. Solution A4 is a reference solution. Solutions A-Mov and B-Mov are the commercially available MOVIPREP solution. Each of solutions A2 to A4 was taken in a dose of 750ml; the MOVIPREP solution was taken in a dose of 1000ml as indicated in the product instructions.

In addition to the investigation formulations intake, the subjects were instructed to take further clear liquid (water). In the case of solutions A2 to A4, they were instructed to take 1750 mL of further clear liquid (875 mL after the evening dose, and 875 mL after the morning dose). In the case of A-Mov, MOVIPREP®, they were instructed to take 1000 mL of further clear liquid (500 mL after the evening dose, and 500 mL after the morning dose).

**Solutions: Part 2:**

**Table 6a**

| Sol'n | PEG3350 /g | $Na_2SO_4$ (anhyd)/g | NaCl /g | KCl /g | Ascorbic acid | Sodium ascorbate | Water to Vol /ml |
|---|---|---|---|---|---|---|---|
| A3 | 100 | 9 | 2.0 | 1.0 | - | - | 750 |

**Table 6b**

| Sol'n | Sachet A | | | | | Sachet B | | | Water to Vol /ml |
|---|---|---|---|---|---|---|---|---|---|
| | PEG3350 /g | $Na_2SO_4$ (anhyd)/g | NaCl /g | KCl /g | $NaHCO_3$ /g | Sodium Ascorbate / g | Ascorbic Acid / g | Magnesium Ascorbate / g | |
| B1 | 40 | - | 3.5 | 2.2 | | 56.6 | - | - | 500 |
| B4 | 40 | 6 | 2.8 | 2.0 | | 33.9 | - | - | 500 |
| B5 | 40 | - | 3.1 | 1.3 | | 33.9 | - | 21.4 | 500 |
| B6 | 29 | 4.8 | 1.4 | 0.9 | 2.2 | - | 23.3 | - | 500 |

The subjects were randomised into four groups (1:1:1:1), and given solution A3 in Table 6a as the evening dose, followed by one of solutions B1, B4, B5 and B6 as the morning dose. Solutions B1, B4 and B5 are solutions of the invention. Solution B6 is a reference solution.

In addition to the investigation formulations intake, the subjects were instructed to take further clear liquid (water). In each case, they were instructed to take 1750 mL of further clear liquid (875 mL after the evening dose, and 875 mL after the morning dose).

**Efficacy:**

The primary variable in the clinical study was the stool weight output generated by the investigational solutions (combined evening and morning dosing on Day 1 and Day 2) over 24 hours from the start of the intake of the evening solution. The reference value of the study was set to a stool weight of

approximately 2500g or greater, which it is desired to be reached in order to demonstrate positive pharmacodynamic effects indicating a potential as a colon cleansing agent.

In addition to the primary trial variable mentioned above, stool output was separately measured and recorded for a) the time between when the subject starts to take the evening dose (17:00 to 18:00 on Day 1) and the time the subject starts to take the morning dose (7am to 8am on Day 2); and b) the time the subject starts to take the morning dose (7am to 8am on Day 2) and midnight on Day 2.

**Results:**

**Table 7a Study Part 1: Stool Weight (g); full analysis set (FAS, N = 81)**

| Treatment | N | 24 hr Median /g | 24 hr Mean /g | 24 hr STD /g |
|---|---|---|---|---|
| A2 + B3 | 20 | 2981.3 | 3021.2 | 599.5 |
| A3 + B3 | 21 | 3493.2 | 3386.1 | 602.74 |
| A4 + B3 | 20 | 2796.80 | 2794 | 688.27 |
| A-Mov + B-Mov | 20 | 3145.95 | 2973.7 | 479.41 |

In the table, the "24 hr Median" is the median stool output in the 24 hours from the time the subject starts to take the evening dose (ie 17:00 to 18:00 on Day 1 to the same time on Day 2); the "24 hr Mean" is the mean of the 24 hour data, and the STD is the standard deviation.

**Table 7b Study Part 1: Stool Weight (g); full analysis set (FAS, N = 81)**

| Treatment | N | pm stool median /g | am stool median /g | | pm stool mean /g | am stool mean /g |
|---|---|---|---|---|---|---|
| A2 + B3 | 20 | 925.8 | 2380.0 | | 867.07 | 2196.9 |
| A3 + B3 | 21 | 1178.5 | 2405.7 | | 1184.34 | 2262.39 |
| A4 + B3 | 20 | 826.7 | 2244.8 | | 832.33 | 2005.25 |
| A-Mov + B-Mov | 20 | 1629.2 | 1536.4 | | 1567.26 | 1453.83 |

The "pm stool median" is the median stool output between the time the subject starts to take the evening dose (17:00 to 18:00 on Day 1) and the time the subject starts to take the morning dose (7 am to 8am on Day 2). The "am stool median" is the median stool output between the time the subject starts to take the morning dose (7am to 8am on Day 2) and midnight on Day 2. The "pm stool mean" and "am stool mean" entries are the corresponding mean values.

It is generally considered that a total stool output of approximately 2500g is required in order to achieve acceptable bowel cleansing. A stool output of approximately 2500g or greater than that is thus indicative that a solution has good potential for use as a bowel cleansing solution. Both A2 + B3 and A3 + B3 resulted in a median stool weight of significantly greater than 2500g. The commercial MOVIPREP® solution also achieved a median stool output of in excess of 2500g, as was to be expected. The stool output was highest for A3 + B3. Solution B3 was therefore selected to be the morning solution for Part 2 of the study. The observed stool output was achieved for MOVIPREP with the ingestion of 2 litres of investigational solution. For the A2 + B3 and A3 + B3 solutions, the mean stool weights were achieved using a total investigational solution volume of 1250ml.

Solutions A2 and A3 were effective in contributing to an effective cleansing with any of the solutions with which they were used. It is seen from the "am stool median" and "pm stool median" figures that the stool output immediately after the ingestion of the A2 and A3 solutions was less copious than after the B solutions. The A2 and A3 solutions contributed to the effective bowel cleansing. Given that the subject will often wish to sleep between taking the first bowel cleansing solution and the second solution, it may be advantageous for the first cleansing solution to result in a slightly lower stool output than the second cleansing solution.

**Table 8a Study Part 2: Stool Weight (g); full analysis set (FAS, N = 80)**

| Treatment | N | 24 hr Median /g | 24 hr Mean /g | 24 hr STD /g |
|---|---|---|---|---|
| A3 + B1 | 20 | 3128.9 | 2898.2 | 856.6 |
| A3 + B4 | 20 | 2546 | 2453.3 | 775.1 |
| A3 + B5 | 20 | 2440.1 | 2501.2 | 1000.3 |
| A3 + B6 | 20 | 2466.8 | 2485.6 | 496.1 |

**Table 8b Study Part 2: Stool Weight (g); full analysis set (FAS, N = 80)**

| Treatment | N | pm stool median /g | am stool median /g | | pm stool mean /g | am stool mean /g |
|---|---|---|---|---|---|---|
| A3 + B1 | 20 | 1170.0 | 2146.4 | | 1087.59 | 1846.41 |
| A3 + B4 | 20 | 1156.5 | 1467.2 | | 1114.64 | 1370.69 |
| A3 + B5 | 20 | 1091.1 | 1448.6 | | 1039.42 | 1574.65 |
| A3 + B6 | 20 | 1210.7 | 1436.2 | | 1163.93 | 1402.64 |

A3+B1 and A3+B4 resulted in a 24 hour median stool output weight of greater than 2500g. For the combination A3+B5, the median stool output was just under 2500g, but the mean stool output was over 2500g. Thus, all of the solution combinations of the invention (A3+B1, A3+B4 and A3+B5) resulted in a 24 hour mean or median stool output weight of greater than 2500g.

Considering the data from tables 7a, 7b, 8a and 8b together, B1, B3, B4 and B5 solutions have been shown to be effective bowel cleansing solutions when used in combination with any other solution with which they were used. The particularly copious stool output seen in the "am stool mean" figures shows that the solutions are especially effective.

In the case of A3+B1, the median stool weight was significantly greater than 2500g. It is again noteworthy that the mean stool weights were achieved using a total investigational solution volume of only 1250ml.

Solution A3 in combination with reference solution B6 resulted in stool output that was not statistically significantly different from 2500g.

Claims:

1. A colon cleansing solution comprising:
a) 60 to 150 g/ litre of an ascorbate component, the ascorbate component being ascorbic acid, one or more salts of ascorbic acid, or a mixture of ascorbic acid and one or more salts of ascorbic acid; and
b) 10 to 200 g per litre polyethylene glycol.

2. A colon cleansing solution as claimed in claim 1 wherein the ascorbate component is ascorbic acid, one or more salts of ascorbic acid selected from sodium ascorbate, potassium ascorbate, magnesium ascorbate and calcium ascorbate, or a mixture thereof.

3. A colon cleansing solution as claimed in claim 1 or claim 2 in which the ascorbate component comprises sodium ascorbate and ascorbic acid.

4. A colon cleansing solution as claimed in claim 3 in which the sodium ascorbate and ascorbic acid are present in a weight ratio of from 1:10 to 10:1.

5. A colon cleansing solution as claimed in claim 1 or claim 2 in which the ascorbate component consists of sodium ascorbate alone.

6. A colon cleansing solution as claimed in any one of claims 1 to 5 comprising:
a) 60 to 150 g/ litre of an ascorbate component;
b) 10 to 200 g per litre PEG having an average molecular weight of 3000 to 4000 Da;
c) sodium chloride and potassium chloride.

7. A colon cleansing solution as claimed in any one of claims 1 to 5 consisting essentially of water and:
a) 60 to 150 g/ litre of an ascorbate component;
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.

8. A colon cleansing solution as claimed in any one of claims 1 to 7 in which the ascorbate component is present at 80 to 120g/litre.

9. A colon cleansing solution as claimed in any one of claims 1 to 8 in which the PEG is present at 30 to 90g/litre.

10. A colon cleansing solution as claimed in any one of claims 1 to 9 which is substantially free from sodium bicarbonate.

11. A composition, optionally presented in two or more parts, for admixture with water to provide a solution as claimed in any one of claims 1 to 10.

12. A dry composition for the preparation of a dose of a solution as claimed in any one of claims 1 to 10 by admixture with water.

13. A dry composition as claimed in claim 12 wherein the dose has a volume of from 400 to 600ml.

14. A composition for admixture with water for the preparation of a colon cleansing solution of claim 1, comprising the following components in the following weight ratios:
a) ascorbate anion provided by ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof: 0.82 to 10.0 parts
b) polyethylene glycol: 1.0 part.

15. A composition as claimed in claim 14 comprising the following components in the following weight ratios:
a) ascorbate anion: 0.82 to 10.0 parts
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.

16. A composition as claimed in claim 14 or claim 15 in which the ascorbate component is present in an amount of 20 to 60g.

17. A composition as claimed in any one of claims 14 to 16 in which the PEG is present in an amount of 15 to 45g.

18. A composition as claimed in any one of claims 14 to 17 which is a dry powder composition.

19. A composition as claimed in any one of claims 14 to 18 which is substantially free from any bicarbonate.

20. A composition as claimed in any one of claims 14 to 19 comprising the following components in the following weight ratios:
a) ascorbate anion: 0.82 to 10.0 parts;
b) PEG having an average molecular weight of 3000 to 4000 Da: 1.0 part; and
c) sodium chloride and potassium chloride;

21. A composition as claimed in any one of claims 14 to 19 consisting essentially of the following components in the following weight ratios:
a) ascorbate anion: 0.82 to 10.0 parts;

b) PEG having an average molecular weight of 3000 to 4000 Da: 1.0 part.

c) sodium chloride and potassium chloride;

e) one or more flavouring agents; and

f) one or more sweeteners.

22. A solution as claimed in any one of claims 1 to 10 for use in cleansing the colon of a mammal.

23. A kit comprising:

- a first colon cleansing solution, and

- a second colon cleansing solution,

the second colon cleansing solution being the solution of any one of claims 1 to 10 in water.

24. A kit as claimed in claim 23 wherein the first colon cleansing solution comprises:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 2.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof.

25. A kit as claimed in claim 23 wherein the first colon cleansing solution consists essentially of water and:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 2.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii) one or more electrolytes;

(iv) one or more flavouring agents; and

(v) one or more sweeteners.

26. A kit comprising:

A) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with water; and

B) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with water;

and optional instructions for use,

the second colon cleansing solution being the solution of any one of claims 1 to 10 in water,

the first solution being different from the second.

27. A kit as claimed in claim 26 comprising:

A) a first component, being a composition for the preparation of a first colon cleansing solution comprising:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 2 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof ;

and

B) a second component, being a composition optionally presented in two or more parts for the preparation of a second colon cleansing solution, the second colon cleansing solution being a solution as claimed in any one of claims 1 to 10,

the first solution being different from the second.

28. A kit as claimed in claim 26 comprising:

A) a first component, being a composition for the preparation of a first colon cleansing solution consisting essentially of:

(i) 70 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 2 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof ;

(iii) one or more electrolytes;

(iv) one or more flavouring agents; and

(v) one or more sweeteners,

and

B) a second component, being a composition optionally presented in two or more parts for the preparation of a second colon cleansing solution, the second colon cleansing solution being a solution as claimed in any one of claims 1 to 10,

the first solution being different from the second.

29. A kit as claimed in claim 26 comprising:

A) a first component being a composition for the preparation of a first colon cleansing solution, the first component comprising:

(i) 52.5 to 187.5 g PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 1.5 to 15 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof

and

B) a second component being a composition optionally presented in two or more parts for the preparation of a second colon cleansing solution, the second colon cleansing solution being a solution as claimed in any one of claims 1 to 10.

30. A kit as claimed in claim 26 comprising:

A) a first component being a composition for the preparation of a first colon cleansing solution, the first component consisting essentially of:

(i) 52.5 to 187.5 g PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 1.5 to 15 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii) one or more electrolytes;

(iv) one or more flavouring agents; and

(v) one or more sweeteners,

and

B) a second component being a composition optionally presented in two or more parts for the preparation of a second colon cleansing solution, the second colon cleansing solution being a solution as claimed in any one of claims 1 to 10.

31. A kit as claimed in any one of claims 26 to 30 which 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.

32. A kit as claimed in claim 31 wherein:

A) the first sachet comprises:

(i) 52.5 to 187.5 g PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 1.5 to 15 g of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii) optionally one or more electrolytes;

(iv) optionally one or more flavouring agents;

(v) optionally one or more sweeteners,

B1) the second sachet comprises:

(i) 5 to 100g PEG having an average molecular weight of 2500 to 4500 Da;

(ii) optionally one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii) electrolytes and/or one or more salts of ascorbic acid; and

B2) the third sachet comprises ascorbic acid,

the one or more salts of ascorbic acid in the second sachet (B1) and the ascorbic acid in the third sachet (B2) together providing 150 to 1000 mmol ascorbate anion.

33. A solution as claimed in any one of claims 1 to 10 for use in cleansing the colon of a subject in combination with a colon cleansing solution comprising:

(i) 130 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da; and

(ii) 8.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof.

34. A solution as claimed in any one of claims 1 to 10 for use in cleansing the colon of a subject in combination with a colon cleansing solution consisting essentially of water and:

(i) 130 to 250 g per litre PEG having an average molecular weight of 2500 to 4500 Da;

(ii) 8.0 to 20 g per litre of one or more alkali metal sulphates, alkaline earth metal sulphates or a mixture thereof;

(iii 1) 1.0 to 3.0 g/L sodium chloride;

(iii 2) 0.5 to 1.5 g/L potassium chloride;

(iv) one or more flavouring agents;

(v) one or more sweeteners.

35. A solution that is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, for use in a method of cleansing the colon of a subject comprising:

- administering to the subject an effective amount of a first cleansing solution; and then after a time interval

- administering to the subject an effective amount of a second cleansing solution,

wherein the second cleansing solution is a solution as claimed in any one of claims 1 to 10, is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion than is present in the second cleansing solution.

36. A solution as for use in a method as claimed in claim 35 wherein the first cleansing solution is a bowel content suspending agent.

37. A solution for use in a method as claimed in claim 35 or 36 wherein the first cleansing solution comprises polyethylene glycol and/or an alkali metal sulphate, an alkaline earth metal sulphate or a mixture thereof.

38. A solution for use in a method as claimed in any one of claims 35 to 37 wherein the first cleansing solution is substantially free from ascorbic acid and salts thereof.

39. A solution for use in a method as claimed in any one of claims 35 to 38 wherein the first and/or second cleansing solution further comprises one or more of:

a) one or more electrolytes;

b) one or more flavouring agents;

c) one or more sweeteners.

40. A solution for use in a method as claimed in any one of claims 35 to 39 wherein the combined volume of the first and second cleansing solutions is less than 2 litres.

41. A solution for use in a method as claimed in any one of claims 35 to 40 wherein the subject takes from 250ml up to 1000ml of the second cleansing solution.

42. A solution for use in a method as claimed in any one of claims 35 to 41 wherein first cleansing solution has a volume of 750ml and the second cleansing solution has a volume of 500ml.

43. A solution as for use in a method as claimed in any one of claims 35 to 42 wherein the measured osmolality of the first cleansing solution is in the range 200 to 1500 mOsmol/kg.

44. A solution as for use in a method as claimed in any one of claims 35 to 43 wherein the measured osmolality of the second cleansing solution is in the range 500 to 2000 mOsmol/kg.

45. A kit comprising:

- a first colon cleansing solution; and

- a second colon cleansing solution,

wherein the second colon cleansing solution is a solution as claimed in any one of claims 1 to 10, is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first colon cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing a lower concentration of ascorbate anion in the first colon solution than is present in the second colon cleansing solution.

46. A kit as claimed in claim 45 wherein the first and/or second solution is as described in any one of claims 35 to 44.

47. A kit as claimed in claim 45 or 46, for use in a method of cleansing the colon of a subject, said method comprising:

- the subject taking an effective amount of a first cleansing solution; and then after a time interval

- the subject taking an effective amount of a second cleansing solution.

48. A kit comprising:

a) a first component, being a composition for the preparation of a first colon cleansing solution by admixture with water; and

b) a second component, being a composition for the preparation of a second colon cleansing solution by admixture with water,

and instructions for use that specify the volume to which each component is to be made up with water,

wherein the second colon cleansing solution, when made up to the instructed specified volume with water, is a solution as claimed in any one of claims 1 to 10, is hyper-osmotic and contains ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof; and wherein the first colon cleansing solution is either substantially free from ascorbic acid and salts thereof, or contains, when made up to the instructed specified volume with water, ascorbic acid, one or more salts of ascorbic acid, or a mixture thereof, in an amount providing, a lower concentration of ascorbate anion in the first colon solution than in the second colon cleansing solution.

49. A kit as claimed in claim 48 wherein one or both of components a) and b) are dry powders.

50. A kit as claimed in claim 48 or 49 wherein the specified volume of water for each solution is less than one litre.

51. A kit as claimed in any one of claims 48 to 50 wherein the specified volume for the first component is 750ml.

52. A kit as claimed in any one of claims 48 to 51 wherein the specified volume for the second component from 500ml.

53. A kit as claimed in any one of claims 48 to 52 wherein the instructions specify that the first colon cleansing solution is ingested first followed, after a time interval, by ingestion of the second colon cleansing solution.

54. A kit as claimed in any one of claims 48 to 53 wherein the first and/or second component is each contained in one or more containers.

55. A kit as claimed in claim 54 wherein the second component is contained in more than one container.

56. A kit as claimed in claim 55 wherein the second component comprises both ascorbic acid and PEG and the ascorbic acid and PEG are contained in separate containers.

57. A kit as claimed in any one of claims 54 to 56 wherein each container is a sachet.

58. A kit as claimed in any one of claims 48 to 57 wherein the first component comprises one dose of the first colon cleansing solution, and the second component comprises one dose of the second colon cleansing solution.

59. A kit as claimed in any one of claims 48 to 58 comprising:

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

b) a second sachet;

c) a third sachet;

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

60. A kit as claimed in claim 59 wherein:

a) the first sachet comprises polyethylene glycol and/or sodium sulphate, optional flavouring and/or optional sweetener;

b) the second sachet comprises polyethylene glycol, and optionally further components including one or more selected from an alkali metal sulphate, an alkaline earth metal sulphate, or a mixture thereof, electrolytes, one or more salts of ascorbic acid, flavouring and sweetener; and

c) the third sachet comprises ascorbic acid and optionally one or more salts of ascorbic acid.