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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 49/04 — A2

(11) International Publication Number: WO 97/30736

(43) International Publication Date: 28 August 1997 (28.08.97)

(21) International Application Number: PCT/GB97/00473

(22) International Filing Date: 20 February 1997 (20.02.97)

(30) Priority Data:
9603547.2 20 February 1996 (20.02.96) GB

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: CONTRAST MEDIUM

(57) Abstract

The invention provides a contrast medium having good lower GI tract coating properties following oral administration. The medium comprises a diagnostically effective amount of a contrast agent together with a viscosity modifier and an osmotic modifier, said modifiers together being present at a weight ratio relative to said agent of at least 1:20.

CONTRAST MEDIUM

Field of the Invention

The invention relates to contrast media, in particular contrast media containing contrast agents, preferably orally administrable particulate contrast agents, for administration into the gastrointestinal tract, and to the use of such contrast media in methods of diagnostic imaging, especially X-ray, CT, magnetic resonance (MR) or ultrasound investigations of the colon.

Background to the Invention

The use of contrast media for enhancing contrast in imaging of the gastrointestinal (GI) tract is well established in several imaging modalities, such as X-ray, CT, ultrasound and MR imaging for example.

In such cases, the contrast medium may be administered either orally or rectally, the administration route generally depending on the section of the GI tract of interest to the physician.

Thus for imaging of the colon or rectum, for example in an investigation for colorectal cancers, polyps or pseudopolyps, rectal administration of contrast is common. However, where certain pathological conditions contraindicate contrast by way of a barium enema, it has been an alternative to administer an oral contrast medium.

Contrast enhanced imaging of the lower portion of the GI tract is generally effected with either volume rendering (in which the contrast medium fills the lumen of the tract) or surface rendering (in which the contrast medium simply coats the mucosa and the tract may be

insufflated with air or another non-toxic gas).

Where the contrast medium is administered by the oral route however, surface rendering of the colon is frequently unsatisfactory with coating being patchy and non-uniform.

More particularly, current formulations do not provide an adequately long-lasting and uniform coating of the colonic mucosa; accordingly, the examination is primarily conducted by examining the initial flow of barium over the mucosa (the "leading edge") and then obtaining confirmatory films (during fluoroscopy and after evacuation and air insufflation). This results in linking the barium administration with the availability of the imaging suite. A formulation with a prolonged and consistent imaging window would permit greater flexibility in patient scheduling.

In addition, examining the "leading edge" of current formulations mandates the use of manipulation which involves patient rotation and the use of compression to highlight flow and edge detail around the area of interest. Use of the "leading edge" technique also increases the chances of missing anatomical lesions since the technique only permits visualisation of a small part of the image field. An improved product with uniform coating characteristics could reduce both study time and patient discomfort by reducing the number of manipulations necessary to obtain a quality study.

The procedure of administering the current barium formulations is also tied to the fluoroscopic portion of the examination. In addition to the time and cost of labor associated with the imaging, fluoroscopic examinations involve higher radiation exposures for both patients and for the technical staff. A formulation

with improved colonic mucosal coating characteristics could serve to reduce fluoroscopic exposure during examinations.

The discomfort associated with the rectal route of administration and with the manipulations involved in imaging give the barium enema an aesthetically displeasing reputation among patients and among physicians. For patients, the outcome is that many patients refuse to undergo this procedure on an elective basis, even when it has documented value as a screening and/or diagnostic procedure. For physicians, the lack of prestige and the need for extensive physical labor to obtain studies of high quality leads to the adoption of more expensive and risky examinations to obtain identical information (eg. colonoscopy).

It is thus an objective of this invention to provide an oral contrast medium with improved surface rendering of the lower portion of the GI tract.

We have now found that such improved surface rendering can be achieved by the formulation of the contrast agent in a composition that contains an osmotic modifier which helps to maintain the hydration balance of the formulation as it passes through the upper GI tract thereby preventing caking of the composition and a mucoadhesive viscosity modifier (eg. a cellulosic agent) which causes the composition to adhere to the walls of the lower GI tract and so reduces pooling of the composition.

Summary of the Invention

Thus viewed from one aspect the invention provides an aqueous diagnostic composition suitable for oral administration for colonic imaging, said composition comprising a diagnostically effective amount of a

contrast agent, eg. an X-ray, CT, MR, ultrasound or radionuclide-containing agent preferably a heavy metal or iodine containing X-ray contrast agent, and especially preferably a particulate agent, together with an amount of an osmotic modifier (eg. a polyol or polyalkyleneglycol) sufficient to prevent caking of the composition in the GI tract and an amount of an organic mucoadhesive viscosity modifier sufficient to cause substantially uniform coating of colonic mucosa by the composition. It is the appropriate balance of an osmotic modifier to enable delivery of the contrast agent to the colon and a viscosity modifier to assure mucoadherence of the contrast agent to the colonic surface that is disclosed herein.

Viewed from another aspect the invention also provides a diagnostic composition comprising a diagnostically effective amount of a contrast agent together with a viscosity modifier and an osmotic modifier, said modifiers together being present at a weight ratio relative to said agent of at least 1:20, said viscosity modifier being selected from the group consisting of polyvinylpyrrolidone, natural gums, polysaccharides and polysaccharide derivatives, and said osmotic modifier being selected from the group consisting of C_3-polyhydric alkanols, polyalkyleneoxides and polyalkyleneoxide derivatives.

These viscosity and osmotic modifiers seem to have a synergistic effect as, by way of example, colloidal inorganic viscosity modifiers did not show such synergy and did not produce efficient coating of the colon in the dog model.

Preferred compositions in accordance with the invention are those having a viscosity in the range of from 2 to 2000 cPs and an osmolality in the range of from 50 to

500 mOsm.

Viewed from a further aspect the invention also provides an improved method of imaging a human or non-human, preferably mammalian, animal subject, which involves administering a contrast medium into the gastrointestinal tract of the subject and generating an image of at least part of said tract, the improvement comprising administering as said contrast medium a composition according to the invention.

Viewed from a yet further aspect the invention provides a process for the preparation of a diagnostic composition, said process comprising admixing a contrast agent together with a viscosity modifier and an osmotic modifier as defined above, in a weight ratio of modifiers to contrast agent of at least 1:20.

Viewed from a still further aspect the invention provides the use of a viscosity modifier and an osmotic modifier for the manufacture of a diagnostic composition according to the invention for use in a method of diagnosis involving imaging of the gastrointestinal tract.

The compositions of the invention may preferably be in a low-viscosity liquid form and especially a ready-to-use form, eg. a storage stable form possibly requiring some shaking but not requiring dilution before use. Such compositions advantageously have viscosities below 500 cP, preferably below 200 cP at ambient temperature (21°C) and contain the contrast agent at concentrations of 5 to 25%, preferably 10 to 20% by weight, for x-ray imaging at concentrations of 0.05 to 10% for CT imaging and at concentrations of 0.001 to 0.5% for MR imaging.

Although the mechanism of action is not fully understood for the described formulations, it was observed that a synergistic interaction between the modifiers occurs resulting in surprising unexpected visco-osmotic properties for the contrast medium which allow high quality imaging of the colon after oral administration of the contrast medium.

Since the appropriate combination of viscosity and osmotic modifiers is effective at delivering an orally administered diagnostic agent to the colon and there providing a uniform coating of the agent on the colonic mucosa, this delivery system is also applicable for the delivery of therapeutic (and by this term prophylatic is included) agents to the walls of lower GI tract and of the colon in particular, via the oral route. Thus viewed from a further aspect the invention also provides an aqueous pharmaceutical composition suitable for oral administration for drug delivery to the lower GI tract of a patient, said composition comprising a therapeutic agent (eg. any of the conventional agents which delivered orally or rectally are taken up through the lining of the gut) together with an organic viscosity modifier present at from 0.1 to 50% w/v and an osmotic modifier present at 0.1 to 50% w/v, the concentrations of said modifiers being sufficient to produce on oral administration a substantially uniform coating of said agent on the patient's colonic mucosa.

Brief Description of the Accompanying Drawings

The invention is illustrated further by the accompanying drawings in which:

Figures 1 and 2 show X-ray images of the GI tract in the dog pre and post oral administration of the formulation of Example 1;

Figures 3, 4, 5 and 6 show X-ray images of the GI tract in the dog after oral administration of the formulation of Example 1 and, by way of comparison, of the commercial barium preparation (50% Liquid Polibar (EZM)) and the commercial iodinated contrast media Gastrografin and Omnipaque (90 mgI/mL);

Figures 2 and 7 show X-ray images of the GI tract in the dog after oral and rectal administration respectively of the formulation of Example 1;

Figures 2 and 8 show X-ray images of the GI tract in the dog after oral administration of the formulation of Example 1 and of an equivalent coloured and flavoured formulation.

Figures 9 and 10 show CT images of the dog after oral administration of the formulation of Example 11; and

Figure 11 shows MR images of the dog after oral administration of the formulation of Example 12.

Detailed Description

The contrast agent in the diagnostic composition of the invention may be any material capable of enhancing image contrast in a diagnostic imaging modality, eg. X-ray, CT, ultrasound, MR, electrical impedance tomography, magnetotomography, SPECT, scintigraphy, etc. The invention is however particularly suited to compositions containing particulate contrast agents or emulsions, eg. inorganic, organic or organometallic particles or, less preferably, molecular aggregates or liposomes. These particulate agents will conveniently be substantially insoluble, or at most poorly soluble, in the composition and in gastric fluid.

The precise nature of the contrast agent will of course depend upon the imaging modality and contrast agents conventionally administered orally or rectally in any modality may be formulated according to the invention. Particularly preferably, for use in X-ray imaging, the contrast agent is an inorganic heavy metal compound, such as barium sulphate or a poorly soluble or essentially water insoluble iodinated organic compound, for example an iodinated compound as discussed in US-A-5330739, US-A-5318768, US-A-5310537, US-A-5308607, US-A-5312616, US-A-5316755, US-A-5260049, US-A-5326553, US-A-5310538, US-A-5260478, US-A-5318767 and US-A-5264610. For use in MR imaging or magnetometry, the contrast agent is preferably an inorganic ferromagnetic, ferrimagnetic, superparamagnetic or paramagnetic material optionally provided with a coating or matrix material, eg. a gastric juice resistant polymeric coating such as a silane or polystyrene. Particles of the type present in Nycomed's ABDOSCAN product or Advanced Magnetics' Biomag M4200 product may thus be used. Alternatively particles of gadolinium oxalate or another relatively insoluble paramagnetic compound may be used. For ultrasound imaging any echogenic material may be used as a contrast agent and for the composition according to the invention these may, for example, be particles of greater or lesser density than gastric fluid, eg. inorganic particulates (eg. barium sulphate) or gas filled synthetic polymer capsules. For scintigraphy and SPECT the contrast agent must obviously contain an appropriate radionuclide, eg in a radionuclide metal ion chelate complex, or a radionuclide containing organic or inorganic material.

Preferably the contrast agent is an inorganic particulate, and especially preferably a barium compound, in particular barium sulphate. Oral administration of barium sulphate compositions according

to the invention has resulted in generation of excellent X-ray images of the lower GI tract and of the colon in particular.

Where the contrast agent is particulate, as with barium sulphate, or where the agent is a water-immiscible liquid which is present in suspensed droplets (ie. as an emulsion), the particle or droplet size is not critical but preferably lies in the range 1 nm to 100 μm, especially 5 nm to 10 μm, particularly 10 nm to 5 μm. Such particles or droplets can be prepared by milling or precipitation or emulsification for example. For image uniformity it is preferred that the particle or droplet size distribution be narrow and preferably substantially monodisperse.

The contrast agent concentration in the compositions of the invention [where these are not concentrates for dilution with water (or another appropriate, preferably aqueous, vehicle) prior to administration] will be selected to be appropriate for the particular contrast agent and imaging modality but will preferably be in the range 0.001 to 95% w/v, preferably 3 to 90% w/v, particularly preferably 5 to 30% w/v and especially preferably 10 to 20% w/v. Too high a concentration of an X-ray contrast agent may make the GI tract too radio-opaque and not allow sufficient delineation of the tract. For X-ray imaging, contrast agent concentration will preferably be 10 to 20% w/v. For MR contrast agents, too high a concentration may result in susceptibility artefacts in the image. For MR imaging, contrast agent concentration will generally be below 1% w/v. For all contrast agents too low a concentration may not provide sufficient contrast enhancement of the image.

The viscosity modifier used according to the invention is preferably a natural gum (eg. guar gum or xanthan gum), polyvinylpyrrolidone or a polysaccharide or polysaccharide derivative. Polysaccharides which are branched, or which carry mono or oligosaccharide side chains or ether derivatives of polysaccharides are preferred. Examples of suitable materials include alginates, pectin, amylopectin, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and microcrystalline cellulose/carboxymethyl cellulose; cellulosic ethers however are preferred.

The viscosity modifier will preferably be a natural gum or a polysaccharide having a molecular weight in the range 25 kD to 2MD.

Such cellulosic ether viscosity modifiers may be any soluble cellulose ether, for example C_{1-6} alkyl or substituted C_{1-6}alkyl, eg. hydroxyalkyl, alkoxyalkyl or carboxyalkyl, ether for example ethyl cellulose, methyl cellulose, propyl cellulose, hydroxyethyl cellulose, methylcarboxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose (and its salts with physiologically tolerable counterions such as alkali metals, eg. sodium), etc. Examples of suitable, commercially available cellulosic ethers include Methocel K4M, K50, K100LVP and E5, Pharmacoat 615 and Avicel CL-611.

While viscosity modifiers capable of producing a range of viscosities, eg. 2-2000 cP at 1.5% w/v in water at ambient temperature, may be used, the lower viscosity modifiers are particularly preferred, eg. ones capable of yielding viscosities as above in the range 2-100 cP, preferably 2 to 60 cP and especially 2-50 cP. In general, the viscosity and the viscosity modifier

content should be kept as low as feasible within the ranges mentioned in order to maximize patient acceptance. The viscosity modifier will generally be used at 0.1 to 50% w/v of the compositions in aqueous ready-to-use form, preferably 0.1 to 10% w/v more especially 1 to 2.5% w/v.

The osmotic modifier used according to the invention is preferably a C_3-polyhydric alcohol (eg. propylene glycol or more preferably glycerine) or a polyalkylene oxide or polyalkylene oxide derivative, for example a polyalkylene glycol.

Such polyalkyleneglycol osmotic modifiers may be homopolymers or co-polymers, eg a block copolymer. Conveniently the alkylene units contain 2 to 6, preferably 2, 3 or 4 carbons and may be the same or different. Thus for example this modifier may be a polyethyleneglycol (PEG), polypropyleneglycol, a poloxamer or a poloxamine. Such polyalkyleneglycols are available commercially in a wide range of molecular weights and preferably those used according to the invention have molecular weights of 150 to 200000 D, especially 200 to 10000 D, and particularly 200 to 4000 D. Examples of suitable commercially available polyalkyleneglycols include PEG types 200, 400, 600, 1450, 3350, 4000, 6000 200K, and 2M. Examples of suitable block copolymers include the pluronics and tetronics, eg pluronic F127 and F108 and tetronic 1508. The polyethylene glycols however are preferred.

The amount of osmotic modifier used is conveniently 0.1 to 50% w/v in the aqueous ready-to-use formulations, preferably 0.1 to 25% w/v (eg. 1 to 25% w/v), more preferably 1 to 10% w/v, especially 2 to 8% w/v. As with the viscosity modifier, the quantity of osmotic modifier will generally be kept as low as feasible.

The osmotic modifier preferably contributes 5 to 500 mOsm, especially 10 to 300 mOsm, and particularly 15 to 150 mOsm, to the overall osmolarity of aqueous formulations according to the invention.

The overall weight ratio of the two modifiers to the contrast agent is, as stated above, at least 1:20. More preferably, particularly with oral barium sulphate compositions, the ratio will be at least 1:10, especially at least 1:5, particularly at least 1:3, and preferably less than 1:1.

The weight ratio of the osmotic modifer to the viscosity modifier is preferably in the range 1:2 to 10:1, especially 1:3 to 8:1, particularly 1:1 to 4:1.

As is demonstrated by the Examples below, the compositions according to the invention achieve good coating of the small bowel and effectively coat the colon, whether administered orally or rectally, and exhibit appropriate colonic residence times. Unlike existing barium sulphate products, they do not exhibit pooling or settling in the small or large intestines, they demonstrate transradiation properties (ie. the ability to allow visualization of multiple overlapping bowel loops) over wide regions, and they demonstrate good edge appearance. By consistently providing high quality mucosal coating the compositions reduce operator work load and interdependencies (ie. the ability to coat the mucosal surface, to provide transradiation and to permit detection of edge appearance) and reduce or eliminate the need for patient manipulation and for excessive radiation exposure for both patients and radiographers and in particular, the need for fluoroscopic examination may be reduced.

X-ray imaging of mammals (eg. dogs) to which the compositions of the invention have been administered orally demonstrated transport to the colon, complete and efficient coating of the ascending, transverse and descending colon, transradiation with good edge delineation without retention in the stomach or small bowel. No manipulation was required to obtain high quality images.

The compositions of the invention may conveniently be administered into the GI tract orally or rectally, in doses of 0.1 to 15 mL/kg bodyweight. However the compositions are especially suited for oral administration and for this route dosages of 1.5 to 15 mL/kg, especially 4 mL to 10 mL/kg, are preferred.

For rectal administration, the volume of composition administered will depend on whether surface rendering or volume rendering is intended. In the former case a volume of 0.1 to 10 mL/kg may be sufficient whereas in the latter case a larger volume of 10 to 15 mL/kg may be required. For surface rendering studies, gas sufflation of the lower portion of the GI tract will generally be desirable.

Following rectal administration, image generation may be effected immediately or within a period of up to 60 minutes. If the composition is administered orally however enough time must be allowed post administration to permit the composition to pass to the desired portion of the gut. Generally, for colonic imaging of an adult human, this will be in the range of 1 to 12 hours.

The imaging technique used may be any of the known imaging modalities. However the compositions of the invention are particularly suitable for use in ultrasound and MR imaging, and especially in a wide

range of X-ray imaging modalities (eg CT, flat-film, digital, fluoroscopy, spiral CT, virtual colonoscopy, etc).

Besides the cellulose ether viscosity modifier, the polyalkyleneglycol osmotic modifier and the contrast agent, the compositions of the invention may contain a liquid carrier medium (eg. water, juice or a water/alcohol mixture) or one or more of the other additives conventional in contrast media formulated for administration into the GI tract, eg. further viscosity or osmotic modifiers, and conventional pharmaceutical or veterinary formulation agents such as preservatives, wetting agents, disintegrants, binders, fillers, stabilizers, flavouring agents, colouring agents, buffers and pH adjusting agents.

The contrast media compositions of the invention may be formulated in a physiologically tolerable aqueous carrier medium (eg. as a suspension, emulsion, solution or dispersion) ready for use or in concentrate form for dilution before use. Concentrates may be diluted, eg. with water, juice, etc. prior to administration. Alternatively, the contrast medium may be formulated in a dry form, eg. in powder, granule, pellet or tablet form for dispersion before use. Ready-to-use aqueous formulations may however be preferred.

The compositions of the invention may contain further (alternative) osmotic and viscosity modifiers. Alternative viscosity modifiers include bentonite, dextrin, veegum, polyvinyl alcohol, carboxymethyl-cellulose sodium, ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose and polyacrylic acids. Alternative osmotic modifiers include polyethylene glycol, glycerin, propylene glycol, sorbitol, mannitol, alpha amino acids and ionic species,

e.g. NaCl, citric acid etc.

The invention will now be described further with reference to the following non-limiting Examples:

Example 1

Barium sulfate formulation containing a viscosity modifier and an osmotic modifier

Ingredient	Concentration (w/v)
Barium Sulfate, USP	15.00%
Polyethylene Glycol, NF 1450	5.00%
Hydroxypropyl methylcellulose 2910, USP*	1.50%
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	1.00%
Simethicone Emulsion, USP 30%	0.33%
Anhydrous Citric Acid, USP	0.19%
Potassium Sorbate, NF	0.15%
Sodium Benzoate, NF	0.12%
Sodium Lauryl Sulfate, NF	0.05%
Anhydrous Saccharin Sodium, USP	0.04%
Purified Water, USP	ad 100 ml

*Available as Methocel E5
(Dow Chemical Company, Midland, Michigan)

X-ray imaging with the above formulation administered orally to dogs demonstrated transport to the colon, complete and efficient coating of ascending, transverse and descending colon, transradiation with good edge appearance, (all of which enhance the diagnostic quality of the radiograph) without retention in the stomach or small bowel. No manipulation was required to obtain high quality images. Pre and post-contrast images appear as Figures 1 and 2 hereto.

The composition of Example 1 is preferably formulated containing color and flavoring agents, eg. FD&C yellow No. 6 Powder 0.015% w/v and Natural and Artificial Citrus Flavour No. 325070 0.5% w/v.

Example 2

Barium sulfate formulation containing a viscosity modifier and an osmotic modifier

Ingredient	Concentration (w/v)
Barium Sulfate, USP	15%
Polyethyleneglycol, NF-1450	2.5-10%
Pharmacoat 615 (hydroxy propyl methyl cellulose)	2.0%
Microcystalline Cellulose and Carboxymethyl Cellulose Sodium, NF*	1.0%
Simethicone emulsion, USP 30%	0.33%
Monohydrate Citric Acid, USP	0.21%
Potassium Sorbate, NF	0.15%
Sodium Benzoate, NF	0.12%
Saccharin Sodium, USP	0.04%
Sodium Laurel Sulphate, NF	0.075%
Purified Water, USP	ad 100 ml

* Available as Avicel CL 611 from FMC Corporation

Example 3

Barium sulfate formulation containing a viscosity modifier and an osmotic modifier

Ingredient	Concentration (w/v)
Barium Sulfate, USP	15%
Polyethyleneglycol, NF-3350	2.5-10%
Pharmacoat 615	2.0%
Microcystalline Cellulose and Carboxymethyl Cellulose Sodium, NF*	1.0%

Simethicone emulsion, USP 30%		0.33%
Monohydrate Citric Acid, USP		0.21%
Potassium Sorbate, NF		0.15%
Sodium Benzoate, NF		0.12%
Saccharin Sodium, USP		0.04%
Sodium Lauryl Sulphate, NF		0.075%
Purified Water, USP	ad	100 ml

Example 4

Magnetic particle formulation

Ingredient	Concentration (w/v)
Polyethylene Glycol, NF 1450	5.00%
Hydroxypropyl Methylcellulose 2910, USP*	1.50%
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	1.00%
Magnetic particles (eg. USPIOs)	0.5%
Simethicone Emulsion, USP 30%	0.33%
Citric Acid, USP	0.19%
Potassium Sorbate, NF	0.15%
Sodium Benzoate, NF	0.12%
Sodium Lauryl Sulfate, NF	0.05%
Saccharin Sodium, USP	0.04%
Purified Water, USP	ad 100 ml

*Available as Methocel E5
(Dow Chemical Company, Midland, Michigan)

Example 5

Comparison of prototype barium sulfate formulations to leading commercial formulations

A side-by-side comparison of the formulation of Example 1 with a 50% (the clinically optimal concentration) commercial barium sulfate suspension and two iodine containing formulations was performed in the canine model following oral administration. Representative of the images generated are Figures 3 (Example 1), 4 (50% Liquid Polibar), 5 (Gastrografin) and 6 (Omnipaque 90 mgI/mL) of the accompanying drawings. The X-ray images were compared for percent colon coating, uniformity, transradiation, edge appearance and mucosal coating of the ascending, transverse and descending colon. The results demonstrated that the performance of the formulation of Example 1 was far superior to that of the prior art, and that the formulation of Example 1 delivered high image quality more consistently and was the only product to meet the needs for diagnostic imaging of the colon via the oral route.

Example 6

Performance reproducibility evaluation of prototype barium sulfate formulations

The reproducibility of image quality and consistent colonic imaging of the formulation of Example 1 per oral and rectal routes were determined using a 20 dog reproducibility study in beagles. The study utilized an oral and rectal crossover design. The results of this study show that the formulation of Example 1 demonstrates highly reproducible, high quality colonic imaging per oral and rectal routes. The X-ray images were compared by three independent evaluators using the

same grading criteria as described in Example 5. The results demonstrated excellent imaging and reproducibility for the formulation.

The colon was defined into six areas: proximal ascending, distal ascending, proximal transverse, distal transverse, proximal descending and distal descending. Table 1 below shows the duration of coating when all areas in the colon were coated, i.e. when all areas were scored as 100% by all three evaluators.

TABLE 1

Summary of length of time of 100% coating of all areas of the colon*
Oral administration
Dogs combined

DURATION	Frequency	Percent
<1 HR**	3	15.0
1-<2 HR	5	25.0
2-<4 HR	9	45.0
4-<5 HR	2	10.0
5-<6 HR	1	5.0

* Timepoints when all evaluators rated the coating as 100%

** 2 dogs had 100% coating of all areas of the colon at 8 hours, which was the final imaging time point in the study. 1 dog had 100% coating of all areas of the colon, except the descending distal colon, from 4 hours through 6 hours. The descending distal colon became 100% coated at 8 hours; however, at 8 hours the mean coating evaluation for the ascending proximal colon was 87%.

Table 2 below shows the mean percentage of colon coated over time.

TABLE 2

Mean percent colon coated over time

Oral administration

Dogs combined

Area of colon	15 min	45 min	75 min	105 min	4 hr	5 hr	6 hr	8 hr
Ascending proximal	0	19	60	83	100	100	100	97
Ascending distal	0	19	64	84	100	100	100	100
Transverse proximal	0	14	63	84	100	100	100	100
Transverse distal	0	10	56	74	98	100	100	100
Descending proximal	0	10	24	43	82	94	98	100
Descending distal	0	10	18	26	73	89	93	100

Example 7

Oral and rectal administration of prototype barium sulfate formulations

The utility of oral and rectal administration in obtaining similar high quality colonic imaging was demonstrated in the study mentioned in Example 6 in which image quality, as evaluated by percent colon coating, uniformity, transradiation, edge appearance and mucosal coating of the ascending, transverse and descending colon, exhibited similar qualities. These qualities were consistent throughout the reproducibility study. An interesting observation was made with retrograde administration of the formulation, in which it performed well in coating the colon and displayed excellent image quality after 5-10 minutes post dosing. This image quality persisted over 60 minutes post rectal dosing.

Example 8

Enhanced residency time of prototype barium sulfate formulations in colonic imaging

A distinct advantage that was observed with the formulation of Example 1 over competitor products was the imaging window seen with oral and rectal administration. Diagnostic imaging persistence of 1-4 hours was observed. Coating of the colon occurred from 4 hours post dosing to at least 8 hours post dosing, in most cases, when the formulation of Example 1 was administered orally to canine dog models. Rectal administration demonstrated high quality imaging, similar to oral administration, over at least a 60 minute window (duration of study). These are demonstrated in the images which appear as Figures 2 (5 hours post dose - oral administration) and 7 (30 minutes post dose - rectal administration) of the accompanying drawings.

Example 9

Addition of flavour and colour enhancers to barium sulfate prototype formulations

Prototype suspensions were formulated containing flavour and colouring agents to enhance patient acceptance and palatability of the dosage form and compared with the formulation of Example 1 for image quality per oral administration. These imaging studies demonstrated that the addition of flavouring and colouring agents did not change the image quality of the formulation which appears to be independent of the flavour and colour used. An exemplary formulation is set out below. Representatives of the images obtained are presented in Figures 2 (formulation of Example 1) and 8 (flavoured and coloured formulations) of the accompanying drawings.

Prototype formulation with flavour and colour:

Ingredient	Concentration (w/v)
Barium Sulfate, USP	15.00%
Polyethylene Glycol, NF 1450	5.00%
Hydroxypropyl Methylcellulose 2910, USP*	1.50%
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	1.00%
Citrus Flavour**	0.50%
Simethicone Emulsion, USP	0.33%
Anhydrous Citric Acid, USP	0.19%
Potassium Sorbate, NF	0.15%
Sodium Benzoate, NF	0.12%
Sodium Lauryl Sulfate, NF	0.05%
Saccharin Sodium, USP	0.04%
FD&C Yellow No. 6	0.01%
Purified Water, USP	ad 100 ml

*Available as Methocel E5
(Dow Chemical Company, Midland, Michigan)
**eg Tastemaker No. 325070

This may be used as either an X-ray contrast agent or an ultrasound contrast agent. Other ethogenic materials, eg. gas-filled particulates or microballoons may be substituted for the barium sulphate.

Example 10

Operator independence

Testing of prototype barium sulfate formulations demonstrated that excellent flat film images of the colon could be performed without manipulation of the subject. In normal GI examination procedures, considerable patient manipulation (ie. rotation, compression, etc.) is required to achieve a diagnostic

image to avoid pooling of the formulation. The formulations described in Examples 1 and 9 above act independently of the operator in obtaining a high quality coating. This effect represents a tremendous advantage over current practice with the biggest advantages in terms of pharmacoeconomics/safety (decreasing fluoroscopy time/exposure and physician time) and consistency of output (which is independent of operator skills).

Example 11

CT-formulation

Ingredient	Concentration (w/v)
Barium Sulfate, USP	3.5%
Polyethylene Glycol, NF 1450	5.00%
Hydroxypropyl Methylcellulose 2910, USP*	1.50%
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	1.00%
Citrus Flavour**	0.50%
Simethicone Emulsion, USP	0.33%
Anhydrous citric Acid, USP	0.19%
Potassium Sorbate, NF	0.15%
Sodium Benzoate, NF	0.12%
Sodium Lauryl Sulfate, NF	0.05%
Saccharin Sodium, USP	0.04%
FD&C Yellow No. 6	0.01%
Purified Water, USP	ad 100 ml

*Available as Methocel E5
(Dow Chemical Company, Midland, Michigan)
**eg Tastemaker No. 325070

CT imaging with the formulation of Example 11, administered orally to dogs demonstrated transport to

the colon with complete and efficient coating with good edge delineation. Additionally, multiple loops of the small intestine demonstrated uniform and complete coating with good edge delineation (see Figures 9 and 10). The compositions are thus clearly useful for both CT and non-CT applications, eg. virtual colonoscopy.

Example 12

MR-formulation

Ingredient	Concentration (w/v)
Gadolinium oxalate	0.005%
Polyethylene Glycol, NF 1450	5.00%
Hydroxypropyl Methylcellulose 2910, USP*	1.50%
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	1.00%
Citrus Flavour**	0.50%
Simethicone Emulsion, USP	0.33%
Anhydrous Citric Acid, USP	0.19%
Potassium Sorbate, NF	0.15%
Sodium Benzoate, NF	0.12%
Sodium Lauryl Sulfate, NF	0.05%
Saccharin Sodium, USP	0.04%
FD&C Yellow No. 6	0.01%
Purified Water, USP	ad 100 ml

*Available as Methocel E5
(Dow Chemical Company, Midland, Michigan)
**eg Tastemaker No. 325070

Magnetic resonance imaging using the formulation of Example 12 administered orally to dogs demonstrated efficient coating of the GI tract with good edge delineation (see Figure 11).

Example 13

Performance of other viscosity modifiers

The following were satisfactorily substituted for the celluloses in the formulation of Example 1 as demonstrated by colonic image quality:

Amylopectin 5.0 mg/mL
Carboxymethylcellulose, sodium NF 0.75 - 2.0 mg/mL
Guar gum NF 1.0 mg/mL
Hydroxypropyl cellulose NF 0.75 - 2.0 mg/mL
Methocel K4M 0.25 mg/mL
Methocel E5 2.5 mg/mL
Methylcellulose NF (25 cP and 1500 cP) 2.0 mg/mL
Avicel CL-611 1.5 mg/mL
Pectin USP 2.5 mg/mL
Povidone (PVP40) USP 2.0 mg/mL
Povidone (PVP 360) USP 2.0 mg/mL
Kollidon 90 2 - 7 mg/mL
Xanthan gum, NF 0.25 mg/mL
Sodium alginate NF 0.5 mg/mL

Example 14

Performance of other osmotic modifiers

The following were satisfactorily substituted for PEG 1450 in the formulation of Example 1 as demonstrated by colonic image quality:

Glycerine USP 5 - 10 mg/mL
Pluronic F108 5.0 mg/mL
PEG 400 2/5 - 10.0 mg/mL
PEG 1450 2.5 - 10.0 mg/mL
PEG 3350 10.0 mg/mL
PEG 20M 10.0 mg/mL

PEG 200K 1 - 3 mg/mL
Tetronic 1508 5.0 mg/mL

Claims

1. A diagnostic composition comprising a diagnostically effective amount of a contrast agent together with a viscosity modifier and an osmotic modifier, said modifiers together being present at a weight ratio relative to said agent of at least 1:20, said viscosity modifier being selected from the group consisting of polyvinylpyrrolidone, natural gums, polysaccharides and polysaccharide derivatives, and said osmotic modifier being selected from the group consisting of C_3-polyhydric alkanols, polyalkyleneoxides and polyalkyleneoxide derivatives.

2. A composition as claimed in claim 1 wherein said viscosity modifier is selected from the group consisting of cellulosic ethers, branched polysaccharides, side chain carrying polysaccharides, natural gums, alginates and polyvinylpyrrolidone.

3. A composition as claimed in claim 1 wherein said viscosity modifier comprises a cellulosic ether.

4. A composition as claimed in any one of claims 1 to 3 wherein said osmotic modifier is selected from the group consisting of alkyleneoxide polymers, alkylene oxide block copolymers and glycerine.

5. A composition as claimed in any one of claims 1 to 4 wherein said osmotic modifier comprises a polyalkyleneglycol.

6. A composition as claimed in claim 1 wherein said viscosity modifier is a cellulosic ether and said osmotic modifier is a polyalkylene glycol.

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7. A composition as claimed in any one of claims 1 to 6 wherein said osmotic modifier has a molecular weight of from 150 to 200000 D.

8. A composition as claimed in any one of claims 1 to 7 in the form of an aqueous solution, suspension or dispersion to the osmolarity of which said osmotic modifier contributes to 5 to 500 mOsm.

9. A composition as claimed in any one of claims 1 to 7 in the form of an aqueous solution, suspension or dispersion to the osmolarity of which said osmotic modifier contributes 15 to 150 mOsm.

10. A composition as claimed in any one of claims 1 to 7 in the form of an aqueous solution, suspension or dispersion containing 1 to 10% w/v of said osmotic modifier.

11. A composition as claimed in any one of claims 1 to 10 wherein said viscosity modifier has a molecular weight of from 25000 to 2000000 D.

12. A composition as claimed in any one of claims 1 to 11 in the form of an aqueous solution, suspension or dispersion to the viscosity of which said viscosity modifier contributes 2 to 2000 cP.

13. A composition as claimed in any one of claims 1 to 11 in the form of an aqueous solution, suspension or dispersion to the viscosity of which said viscosity modifier contributes 2 to 60 cP.

14. A composition as claimed in any one of claims 1 to 13 in the form of an aqueous solution, suspension or dispersion containing 0.1 to 10% w/v of said viscosity modifier

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15. A compostion as claimed in any one of claims 1 to 14 wherein said contrast agent is particulate.

16. A composition as claimed in any one of claims 1 to 15 wherein said contrast agent is a heavy metal or iodine containing X-ray contrast agent.

17. A composition as claimed in claim 16 wherein said contrast agent is barium sulphate.

18. A composition as claimed in claim 17 wherein said modifiers are together present in a weight ratio relative to the barium sulphate of at least 1:5.

19. A composition as claimed in any one of claims 1 to 18 having a viscosity in the range 2 to 100 cP.

20. A composition as claimed in any one of claims 1 to 19 in ready-to-use form suitable for oral administration.

21. A composition as claimed in any one of claims 1 to 20 wherein said osmotic modifier and said viscosity modifier are present at a weight ratio of 1:2 to 10:1.

22. An aqueous diagnostic composition suitable for oral administration for colonic imaging, said composition comprising a diagnostically effective amount of a contrast agent together with an amount of an osmotic modifier sufficient to prevent caking of the composition in the upper GI tract and an amount of an organic mucoadhesive viscosity modifier sufficient to cause substantially uniform coating of colonic mucosa by the composition.

23. In a method of imaging a human or non-human animal subject, which involves administering a contrast medium

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into the gastrointestinal tract of the subject and generating an image of at least part of said tract, the improvement comprising administering as said contrast medium a composition as claimed in any one of claims 1 to 22.

24. A method as claimed in claim 23 wherein said image is an X-ray image.

25. A method as claimed in claim 23 wherein said image is an MR image.

26. A method as claimed in claim 23 wherein said image is an ultrasound image.

27. A process for the preparation of a diagnostic composition, said process comprising admixing a contrast agent together with a viscosity modifier and an osmotic modifier as defined in claim 1, in a weight ratio of modifiers to contrast agent of at least 1:20.

28. The use of a viscosity modifier and an osmotic modifier for the manufacture of a diagnostic composition as defined in any one of claims 1 to 22 for use in a method of diagnosis involving imaging of the gastrointestinal tract.

29. An aqueous pharmaceutical composition suitable for oral administration for drug delivery to the lower GI tract of a patient, said composition comprising a therapeutic agent together with an organic viscosity modifier present at from 0.1 to 50% w/v and an osmotic modifier present at 0.1 to 50% w/v, the concentrations of said modifiers being sufficient to produce on oral administration a substantially uniform coating of said agent on the patient's colonic mucosa.

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FIG. 1.

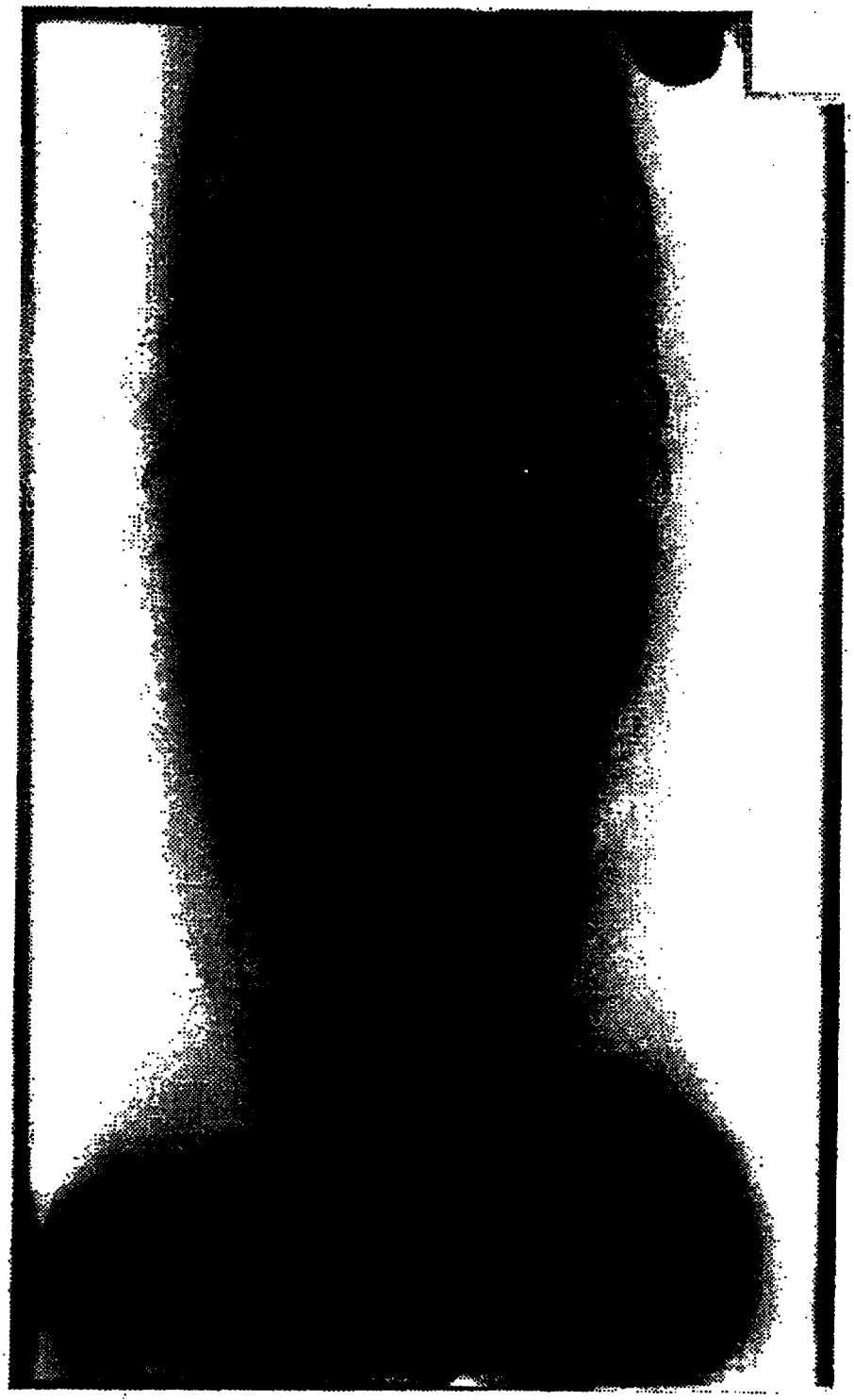


FIG. 2.



FIG. 3.



FIG. 4.



FIG. 5.

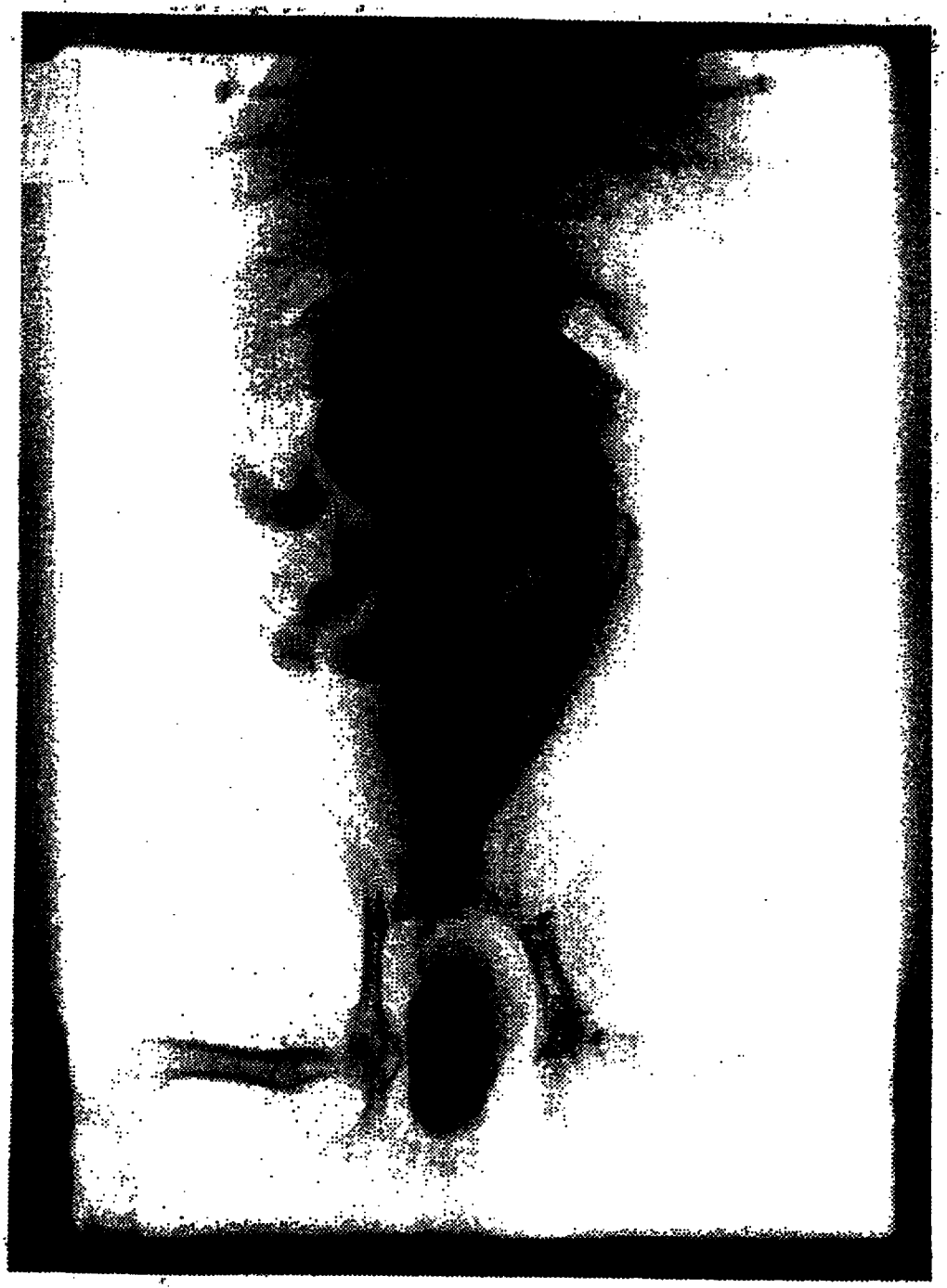


FIG. 6.



FIG. 7.



FIG. 8.



FIG. 9.



FIG. 10b.

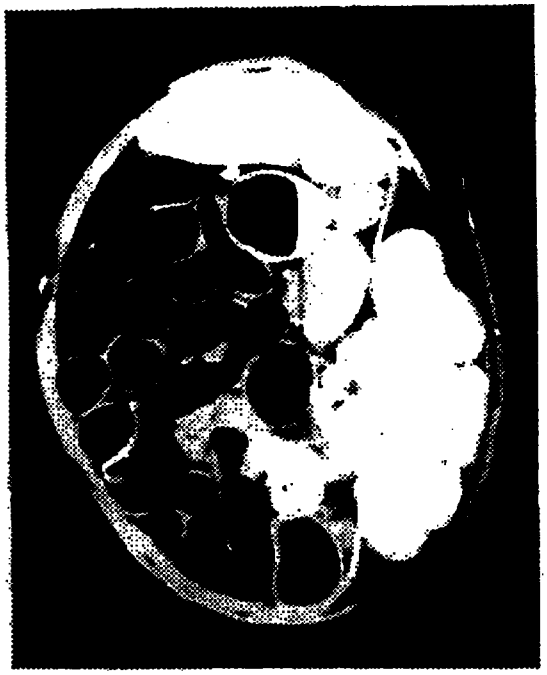


FIG. 10d.



FIG. 10a.



FIG. 10c.

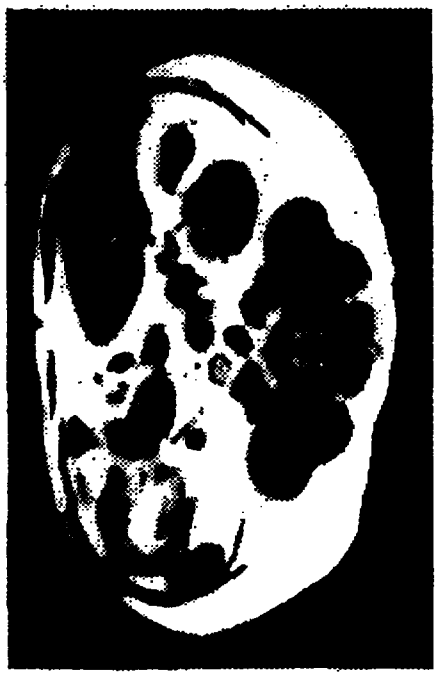


FIG. 11a.



FIG. 11b.



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Claims

1. A diagnostic composition comprising a diagnostically effective amount of an inorganic particulate contrast agent together with a viscosity modifier and a polyalkylene glycol osmotic modifier, said modifiers together being present at a weight ratio relative to said agent of at least 1:20, and said viscosity modifier being selected from the group consisting of polyvinylpyrrolidone, natural gums, polysaccharides and polysaccharide derivatives.

2. A composition as claimed in claim 1 wherein said viscosity modifier is selected from the group consisting of cellulosic ethers, branched polysaccharides, side chain carrying polysaccharides, natural gums, alginates and polyvinylpyrrolidone.

3. A composition as claimed in claim 1 wherein said viscosity modifier comprises a cellulosic ether.

4. A composition as claimed in any one of claims 1 to 3 wherein said osmotic modifier comprises a polyethylene glycol.

5. A composition as claimed in claim 1 wherein said viscosity modifier is a cellulosic ether.

6. A composition as claimed in any one of claims 1 to 5 wherein said osmotic modifier has a molecular weight of from 150 to 200000 D.

7. A composition as claimed in any one of claims 1 to 6 in the form of an aqueous solution, suspension or dispersion to the osmolarity of which said osmotic modifier contributes to 5 to 500 mOsm.

* C L M S *

8. A composition as claimed in any one of claims 1 to 6 in the form of an aqueous solution, suspension or dispersion to the osmolarity of which said osmotic modifier contributes 15 to 150 mOsm.

9. A composition as claimed in any one of claims 1 to 6 in the form of an aqueous solution, suspension or dispersion containing 1 to 10% w/v of said osmotic modifier.

10. A composition as claimed in any one of claims 1 to 9 wherein said viscosity modifier has a molecular weight of from 25000 to 2000000 D.

11. A composition as claimed in any one of claims 1 to 10 in the form of an aqueous solution, suspension or dispersion to the viscosity of which said viscosity modifier contributes 2 to 2000 cP.

12. A composition as claimed in any one of claims 1 to 10 in the form of an aqueous solution, suspension or dispersion to the viscosity of which said viscosity modifier contributes 2 to 60 cP.

13. A composition as claimed in any one of claims 1 to 12 in the form of an aqueous solution, suspension or dispersion containing 0.1 to 10% w/v of said viscosity modifier.

14. A composition as claimed in any one of claims 1 to 13 wherein said contrast agent is a heavy metal or iodine containing X-ray contrast agent.

15. A composition as claimed in claim 14 wherein said contrast agent is barium sulphate.

* C L M S *

16. A composition as claimed in claim 15 wherein said modifiers are together present in a weight ratio relative to the barium sulphate of at least 1:5.

17. A composition as claimed in any one of claims 1 to 16 having a viscosity in the range 2 to 100 cP.

18. A composition as claimed in any one of claims 1 to 17 in ready-to-use form suitable for oral administration.

19. A composition as claimed in any one of claims 1 to 18 wherein said osmotic modifier and said viscosity modifier are present at a weight ratio of 1:2 to 10:1.

20. An aqueous diagnostic composition suitable for oral administration for colonic imaging, said composition comprising a diagnostically effective amount of an inorganic particulate contrast agent together with an amount of a polyalkylene glycol osmotic modifier sufficient to prevent caking of the composition in the upper GI tract and an amount of an organic mucoadhesive viscosity modifier sufficient to cause substantially uniform coating of colonic mucosa by the composition.

21. In a method of imaging a human or non-human animal subject, which involves administering a contrast medium into the gastrointestinal tract of the subject and generating an image of at least part of said tract, the improvement comprising administering as said contrast medium a composition as claimed in any one of claims 1 to 20.

22. A method as claimed in claim 21 wherein said image is an X-ray image.

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23. A method as claimed in claim 21 wherein said image is an MR image.

24. A method as claimed in claim 21 wherein said image is an ultrasound image.

25. A process for the preparation of a diagnostic composition, said process comprising admixing an inorganic particulate contrast agent together with a viscosity modifier and a polyalkylene glycol osmotic modifier as defined in claim 1, in a weight ratio of modifiers to contrast agent of at least 1:20.

26. The use of a viscosity modifier and a polyalkylene glycol osmotic modifier for the manufacture of a diagnostic composition as defined in any one of claims 1 to 20 for use in a method of diagnosis involving imaging of the gastrointestinal tract.

27. An aqueous pharmaceutical composition suitable for oral administration for drug delivery to the lower GI tract of a patient, said composition comprising a therapeutic agent together with an organic viscosity modifier present at from 0.1 to 50% w/v and a polyalkylene glycol osmotic modifier present at 0.1 to 50% w/v, the concentrations of said modifiers being sufficient to produce on oral administration a substantially uniform coating of said agent on the patient's colonic mucosa.

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