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(54) Title: INDIRECT CHROMOENDOSCOPY WITH AN ORAL INDIGO CARMINE BASE PREPARATION

(57) Abstract: Indirect chromoendoscopy is performed by providing a subject with an orally administered composition which includes indigo carmine dye mixed with polyethylene glycol (PEG). Preferably, the subject ingests at least 160 mg of indigo carmine prior to the endoscopic procedure. This is accomplished by ingesting 1 ml to 6L of a premixed or reconstituted indigo carmine and PEG composition up to twenty four hours prior to the endoscopic procedure.

INDIRECT CHROMOENDOSCOPY WITH AN ORAL INDIGO CARMINE BASE PREPARATION

FIELD OF THE INVENTION

The invention relates to a pharmaceutical composition comprising indigo carmine mixed with polyethylene glycol and a method for staining the alimentary or gastrointestinal tract in preparation for a chromoendoscopic procedure.

BACKGROUND OF THE INVENTION

Colonoscopy is currently the preferred method for colon cancer screening. This procedure is used to examine the surface of the gastrointestinal tract for abnormalities, such as polyps consisting of abnormal growth into the lumen. When detected, these polyps can be removed thus decreasing the risk of colon cancer by an estimated 75 to 90% (Davila et al., 2006). However, the colonoscopy miss rate can be over 10% (Pickhardt et al., 2004). Cancers diagnosed after a colonoscopy, also called interval cancers, have multiple possible causes including a different biology than non-interval cancers and factors related to the procedure itself. Among procedural causes, missed lesions are thought to play a large role (Cooper et al., 2011; Pohl et al., 2010; Faiss S., 2011). There has been significant focus on flat lesions and specifically sessile serrated adenomas and their possible role in interval cancer. Flat polyps especially the sessile serrated adenomas are difficult to detect and may evolve more rapidly into cancer (Anderson J., 2011; Leggett et al., 2010).

For colonoscopy to continue to be the preferred method for colon cancer screening, its sensitivity must improve. Panchromoendoscopy using dyes including Indigo carmine or Methylene blue sprayed directly onto the surface of the colon has been shown to increase the sensitivity. However chromoendoscopy has not been widely adopted because it can be cumbersome and time-consuming (Coe et al., 2012). Chromoendoscopy remains the gold standard for polyp detection and should theoretically be performed routinely (Brown S. and Baraza W., 2010). However, time constraints continue to dictate that chromoendoscopy is employed only selectively.

Indirect chromoendoscopy offers the potential for more efficient use of chromoendoscopy. With indirect chromoendoscopy, the dye is administered orally thereby

eliminating the time spent spraying the colon. Indirect chromoendoscopy has been attempted in the past with giving 100 mg of oral indigo carmine in the form of a capsule or powder before ingestion of the oral preparation (Mitooka et al., 1992). However, this method has not been adopted as it does not provide enough staining to improve polyp detection rate (Araujo et al., 2002). There is a need for new methods to enhance staining during chromoendoscopy in a more time-efficient and convenient manner.

SUMMARY OF THE INVENTION

Embodiments of the invention relate to a pharmaceutical composition comprising indigo carmine mixed with polyethylene PEG and a method for staining of the alimentary or gastrointestinal tract. The invention allows for more efficient performance of chromoendoscopy. Dye staining with this solution can significantly enhance lesion detection. The routine use of this technology will improve polyp detection rates and make its use a new standard of care.

Disclosed herein are pharmaceutically acceptable compositions of indigo carmine premixed with PEG. The composition may further comprise at least one of the following: sodium (Na), potassium (K), chloride (Cl), Bicarbonate (HCO_3), sulfate (SO_4) or simethicone. In some embodiments, the solution may also contain substances to prevent water absorption, improve palatability, decrease fluid shifts, decrease foaming, alter gastrointestinal motility, alter absorption, and improve tolerability. Preferably, the indigo carmine dye comprises at least 0.64 wt%.

In some embodiments, the solution comprising indigo carmine and PEG is orally administered in one session four to twenty-four hours before an endoscopic procedure. In other embodiments, the indigo carmine solution is orally administered in two sessions, the first session four to twenty-four hours before said endoscopic procedure and the second session one to four hours before said endoscopic procedure. Preferably, the dose provided to a subject is at least 160 mg of indigo carmine dye, and preferably 160-480 mg of indigo carmine dye. Preferably, the dose is provided with 1 ml to 6 liters of PEG.

DESCRIPTION OF THE FIGURE

Figure 1 is a flow diagram illustrating an exemplary chromoendoscope procedure according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Indigo carmine is FDA approved for use as a food colorant. Specifically, the FDA certifies up to 2 mg/kg of daily intake of indigo carmine, and there are no reports of toxicity from oral administration. If a 2L solution of 0.008% of indigo carmine is ingested it would amount to a dose of 160 mg. Most of the oral solution will reach the colon intact. In rat studies, 3% of the dye taken orally was absorbed (Lethco et al., 1966). Data suggest that the food colorant absorbed in humans will be cleared very rapidly from circulation (Oravisto K., 1957). The combination of low levels of absorption, rapid clearance, and no known toxicity together make it unlikely that this food colorant would reach clinically significant concentrations, and thus indigo carmine dye will be well tolerated.

As further support of the safety of indigo carmine given for indirect chromoendoscopy, it is estimated that absorption through oral administration according to the methods of the present invention will lead to lower concentrations than what is currently used and accepted during intravenous administration. When used intravenously, indigo carmine is given in doses of 20 mg and 40 mg to diagnose ureteral injuries. Although there are rare case reports of hypotension, hypertension and anaphylaxis with the intravenous use of indigo carmine, causality has not been established (Jeffords et al., 1977; Shir et al., 1993; Gousse et al., 2000). If higher doses of oral indigo carmine are necessary to perform adequate panchromoendoscopy, they will be tolerated with minimal to no side effects.

Polyethylene Glycol (PEG) is a generic substance (sometimes referred to as polyethylene oxide or polyoxyethylene) used in multiple industries including colonic cleansing solutions. PEG is a well recognized excipient used in the pharmaceutical industry, and is also a well recognized constituent in a number of laxatives (e.g., MiraLAX and Dulcolax) PEG is available in substituted and unsubstitute forms. Indigo carmine has been used to stain colonic polyps for better identification, and studies have shown that if sprayed topically during an endoscopic procedure, it improved detection of abnormalities. Combining both materials and having the patient ingest them will pre-stain the colon for colonoscopy and save time, as spraying is not usually done because it is cumbersome and time consuming and does not lead to uniform staining. The present invention will help endoscopists perform chromoendoscopy more efficiently, without the need to spend time spraying the dye, and help to improve detection of

polyps. Endoscopists can be provided with educational material and videos of examples of how to use the composition.

Embodiments of the invention thus provide methods of staining the alimentary or gastrointestinal (GI) tract of a subject. The methods comprise orally administering to a subject a composition comprising PEG mixed with indigo carmine dye. The premixed composition, which provides higher than normal doses of indigo carmine, produces significantly better staining of the alimentary and gastrointestinal tract as compared to more traditional methods. This premixed composition thus allows for increased visualization of colonic lesions.

Embodiments of the invention provide premixed compositions which are in liquid or reconstitutable form (e.g., assume a liquid format on the addition of water or aqueous fluid) comprising indigo carmine dye mixed with PEG. The compositions are orally ingestible and may contain one or more other ingredients, e.g. salts and ionized forms thereof, (e.g. Na^+, K^+, Cl^-, $HC0_3^-$, $S0_4^{2-}$, etc). The composition may also contain other beneficial substances such as flavorings, colorants, buffering agents, thickeners, wetting agents, etc. In exemplary embodiments, the composition is formulated to provide indigo carmine at doses ranging from 160 mg to 10 g (and in certain embodiments, 150-500 mg or 160 mg to 480 mg and other comparable ranges). The indigo carmine dye is mixed with PEG and one or more of sodium, potassium, chloride, bicarbonate, SO_4, and the anti-foaming agent simethicone, and preferably has an osmolality between 270 and 290. The constituents have concentrations within the following ranges:

Na^+ (mEq/L)	0 to 150
K^+ (mEq/L)	0 to 100
Cl^- (mEq/L)	0 to 100
HCO_3^- (mEq/L)	0 to 100
SO_4^{2-} (mEq/L)	0 to 100
PEG (gm/L)	0 to 200
Simethicone (gm/L)	0 to 1500

The molecular weight of the PEG can vary from low molecular weights (e.g., 300-400 MW) to high molecular weights (5000 MW and above), and the liquid composition used in the invention could include a mixture of PEG at different molecular weights.

The indigo carmine and PEG composition can be provided in a container to be mixed before use with water. The indigo carmine and PEG composition can, for example, be administered in one or two sessions based on the patient's and/or healthcare provider's preference and indication. In a non-split preparation protocol, up to 6 liters of the solution may be consumed in one session four to twenty-four hours before the endoscopic procedure. In a split preparation protocol, a portion of the preparation with or without indigo carmine may be consumed four to twenty-four hours before the procedure and a second portion may be consumed one to four hours before the procedure. Each portion of the split preparation can range from 1 ml to 6 liters (and in some embodiments 100 ml to 4 liters or 250 ml to 2 liters, and other comparable ranges).

Capsule chromoendoscopy has been attempted in the past with mixed results. Mitooka and colleagues attempted oral administration of 100 mg of indigo carmine powder before the colonic prep and found it to give a good effect in 80% of the cases on the right colon and 50% of the left colon. No side effects were observed (Mitooka et al., 1992). Araujo and colleagues administered 100 mg of oral indigo carmine in a capsule before the colonic prep and found that it was ineffective in staining the entire colon in over 90% of the cases (Araujo et al., 2002).

Embodiments of the present invention provide methods to enhance the staining when compared to capsule chromoendoscopy. Unlike capsule chromoendoscopy, the indigo carmine dye is premixed with PEG. The premixed indigo carmine and PEG composition can also be reconstituted from a powdered or dried form. Providing a mixed solution assures distribution of the indigo carmine dye in the gastrointestinal tract. Also, having higher doses of indigo carmine than previously used, allows for better staining results. The mixture can be administered starting twenty-four hours before the endoscopic procedure (e.g. colonoscopy). Volumes of the solution orally administered can range from 1-5 ml to 6 liters (and in some embodiments 100 ml to 4 liters or 250 ml to 2 liters, and other comparable ranges).

Embodiments of the invention also provide methods of performing endoscopic procedures which require or for which it is beneficial to stain tissue or cells that are to be examined. The methods include administering to a subject (e.g. orally or by rinsing or washing) a

composition comprising PEG and indigo carmine dye, and then carrying out the endoscopic procedure. The endoscopic procedures include but are not limited to: investigation of any portion of the GI tract, including the esophagus, stomach and duodenum (esophagogastroduodenoscopy); small intestine (enteroscopy); large intestine/colon (colonoscopy, sigmoidoscopy); bile ducts, rectum (rectoscopy) and anus (anoscopy) (both also referred to as "proctoscopy"). However, other applications of the technology are also possible in which tissues or cells are exposed to the composition (e.g. via washing or rinsing with a PEG-indigo carmine composition) and stained thereby. In such embodiments, the composition is not necessarily ingestible or "food grade" but is physiological compatible. Cells that may be stained and examined include tissues or cells of the respiratory tract, the nose (rhinoscopy), the lower respiratory tract (bronchoscopy), the ear (otoscopy), the urinary tract (cystoscopy), the female reproductive system (gynoscopy), the cervix and/or vagina (colposcopy), the uterus (hysteroscopy), the fallopian tubes (falloposcopy), and normally closed body cavities (e.g. accessed through a small incision) such as the abdominal or pelvic cavity (laparoscopy), the interior of a joint (arthroscopy), organs of the chest (thoracoscopy and mediastinoscopy), etc.

Embodiments of the invention also include methods of identifying abnormal cells by exposing cells, tissue, organs, etc. suspected of containing abnormal cells or growths (e.g. cancerous or precancerous cells, polyps, tumors, etc.). The methods include exposing cells, tissue, organs, etc. that may contain such abnormalities to the composition of the invention, viewing and/or imaging the stained cells, tissue, organs, etc., and concluding whether or not the stained cells are normal or abnormal. The methods may include steps of comparing the viewed or imaged cells to reference cells (e,g. normal cells and/or known abnormal or diseased cells), in order to recognize similarities and differences, then concluding whether or not the stained cells are normal or abnormal based on the comparison.

While invention has been described in its preferred embodiments, those of skill in the art will recognize the invention can be practiced with variations within the spirit and scope of the appended claims.

REFERENCES

Throughout this application, various references describe the state of the art to which this invention pertains. The disclosures of these references are hereby incorporated by reference into the present disclosure.

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CLAIMS

1. A pharmaceutical composition for use in staining of the alimentary or gastrointestinal tract comprising indigo carmine dye mixed with polyethylene glycol (PEG) that provides an administered dose of at least 160 mg of said indigo carmine dye in the form of a reconstitutable powder or premixed solution.

2. A pharmaceutical composition comprising indigo carmine dye mixed with PEG in liquid or reconstitutable form wherein said indigo carmine dye comprises at least 0.64 wt%.

3. The composition of claim 1 further comprising at least one of the following: sodium (Na), potassium (K), chloride (Cl), Bicarbonate (HCO_3), sulfate (SO_4) or simethicone.

4. The composition of claim 1 further comprising at least one of the following: electrolytes, flavorings, colorants, buffering agents, thickeners or wetting agents.

5. The composition of claim 1 wherein said dose of indigo carmine dye ranges from 160 mg to 10 g in 1 ml to 6 liters of PEG.

6. A method for staining of the alimentary or gastrointestinal tract comprising the step of:

orally administering to a subject a pharmaceutical composition comprising indigo carmine dye pre-mixed with PEG.

7. The method of claim 6, wherein said orally administering step provides an administered dose of at least 160 mg of said indigo carmine dye.

8. The method of claim 6, wherein said pharmaceutical composition comprises at least 0.64 wt% of said indigo carmine dye.

9. The method of claim 6, wherein said composition further comprises at least one of the following: sodium (Na), potassium (K), chloride (Cl), Bicarbonate (HCO_3), sulfate (SO_4) or simethicone.

10. The method of claim 6, wherein said composition further comprises at least one of the following: electrolytes, flavorings, colorants, buffering agents, thickeners or wetting agents.

11. The method of claim 7, wherein said dose of indigo carmine dye ranges from 160 mg to 10 g in 1 ml to 6 liters of PEG.

12. The method of claim 6, wherein said orally administering step includes a step of reconstituting said pharmaceutical composition into a liquid format.

13. A method for performing a chromoendoscopic procedure comprising the steps of:

orally administering to a subject a pharmaceutical composition comprising indigo carmine dye mixed with polyethylene glycol that provides an administered dose of at least 160 mg of said indigo carmine dye; twenty-four hours after said orally administering step, performing a chromoendoscopic procedure.

14. The method of claim 13, wherein said orally administering step is performed in one session four to twenty-four hours before said step of performing a chromoendoscopic procedure.

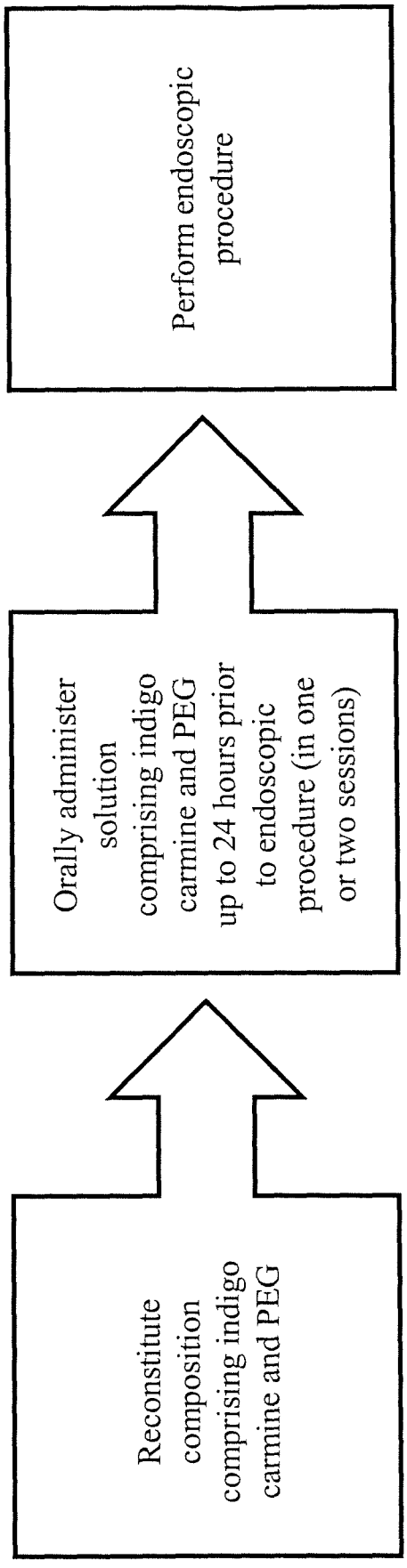
15. The method of claim 13, wherein said orally administering step is performed in two sessions, a first of said two sessions being performed four to twenty-four hours before said step of performing said chromoendoscopic procedure, and a second of said two sessions being performed one to four hours before said step of performing said chromoendoscopic procedure.

16. The method of claim 13, wherein said composition further comprises at least one of the following: sodium (Na), potassium (K), chloride (Cl), Bicarbonate (HCO_3), sulfate (SO_4) or simethicone.

17. The method of claim 13, wherein said composition further comprises at least one of the following: electrolytes, flavorings, colorants, buffering agents, thickeners or wetting agents.

18. The method of claim 13, wherein said dose of indigo carmine dye ranges from 160 mg to 10 g in 1 ml to 6 liters of PEG.

19. The method of claim 13, wherein said orally administering step includes a step of reconstituting said composition into a liquid format.


Perform endoscopic procedure
Orally administer solution comprising indigo carmine and PEG up to 24 hours prior to endoscopic procedure (in one or two sessions)
Reconstitute composition comprising indigo carmine and PEG

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/016488

A. CLASSIFICATION OF SUBJECT MATTER

A61K 49/00(2006.01)i, A61K 49/10(2006.01)i, A61K 9/14(2006.01)i, A61K 9/08(2006.01)i, A61K 47/34(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 49/00; A61K 9/00; G01N 1/30; A61K 49/10; A61K 9/14; A61K 9/08; A61K 47/34

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: indigo carmine dye, polyethylene glycol, chromoendoscopy, colon cancer, oral

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011-110347 A2 (GIULIANI INTERNATIONAL LIMITED) 15 September 2011 See abstract; paragraphs [0048]-[0052]; and claims 1 and 19.	1-5
A	US 2012-0251458 A1 (DE SOUSA MARTINS, D. et al.) 04 October 2012 See abstract; and claims 11-17.	1-5
A	US 8545811 B2 (MORO, L. et al.) 01 October 2013 See abstract; and columns 10 and 11.	1-5
A	HURLSTONE, D. P. et al., `Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy`, Gut, 2004, Vol. 53, No. 3, pp. 376-380 See the whole document.	1-5
A	LECOMTE, T. et al., `Chromoendoscopic colonoscopy for detecting preneoplastic lesions in hereditary nonpolyposis colorectal cancer syndrome`, Clinical Gastroenterology and Hepatology, 2005, Vol. 3, No. 9, pp. 897-902 See the whole document.	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2015 (24.04.2015)	**27 April 2015 (27.04.2015)**

Name and mailing address of the ISA/KR
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/016488

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 6-19
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 6-19 pertain to methods for treatment of the human body by therapy, as well as diagnostic methods practiced on the human body, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/016488

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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