SPECIFICATION

Carminative Preparations containing peppermint oil

The present invention relates to carminative preparations containing peppermint oil. It provides novel preparations for selectively administering a carminative in the intestine.

Functional bowel disorders characterised by recurrent intestinal distension, colicky pain, and intermittent change in bowel habit are common. They are frequently described as "irritable colon syndrome", which is a diagnosis arrived at after exclusion of other organic pathologies. This group of conditions may not be a single group with a simple basis of one aetiological factor but it is probably the most common single clinical problem relating to disorders of the large bowel. The condition tends to be chronic, with relapses even after a time of normal health.

Irritable colon syndrome and certain other intestinal disorders such as diverticular disease and spastic colon could be relieved by administering to the intestine a muscle relaxant and/or antispasmodic drug. However, no wholly satisfactory treatment of these disorders has been available. It is therefore an object of the present invention to provide a relatively inexpensive, easily administered and effective treatment for these disorders.

Peppermint oil is an ethereal oil obtained from plants of the genus *Labiatae* and has been known as a medicament since the very beginning of pharmacy. It exerts a mild irritant action on the mucous membranes of the mouth and digestive tract and is a mild expectorant. In particular, it is used as a carminative (i.e. muscle relaxant with anti-spasmodic effect) after meals and for the relief of gastric discomfort and of flatulent colic and also to counteract the griping action of purgatives (see "The Extra Pharmacopoeia, 27th Edition, Martindale).

When administered for its known carminative effect, peppermint oil is taken orally in a form which is effective in the stomach. The dose administered is limited by its irritant action on the mucous membranes and particularly by action on the gastro-oesophageal spincter. Thus, although the essential oil so administered passes into the small intestine, and eventually into the colon, the amount is insufficient to produce any substantial carminative effect in the intestine and certainly insufficient for the effective treatment of irritable colon syndrome, diverticular disease or spastic colon. To the best of our knowledge the possibility of using peppermint oil for treatment of such intestinal disorders has been dismissed, perhaps subconsciously, because of the dose limitations imposed by the effect on the mucous membranes of the oesophagus and stomach and/or gastro-oesophageal spincter. The fact of the matter is that our investigations indicate that, despite the long known carminative action of peppermint oil and the long felt need for a readily administered and effective treatment for irritable colon syndrome, there has been no previous proposal to use peppermint oil for inducing a significant carminative effect in the intestine.

We have found that peppermint oil provides a readily administered and effective treatment for irritable colon syndrome when presented as an enterically coated hard gelatin capsule.

The present invention provides in one aspect thereof an enterically coated hard gelatin capsule containing 0.05 ml to 0.5 ml peppermint oil.

The presently preferred peppermint oil is Peppermint Oil (B.P.) which contains 4 to 10% w/w esters calculated as menthyl acetate, not less than 44% w/w free alcohols calculated as menthol and 15 to 32% w/w ketonic compounds calculated as menthone. It is a colourless, pale yellow or greenish-yellow liquid obtained by distillation and, if necessary, subsequent rectification from the fresh flowering tops of the plant *Mentha × piperita* (Labiatae).

Enteric coatings are widely used in the pharmaceutical industry and are formed of substances which are relatively insoluble in the acid medium of the stomach but disintegrate in the medium of the small intestine. A preferred enteric coating is a cellulose acetate phthalate coating. Other suitable coatings include enteric coating lacquers based on polymeric methacrylates.

Usually the peppermint oil will be administered in a daily dose of 0.15 ml to 3.0 ml, especially 0.6 ml to 2.4 ml and particularly about 1.2 ml. The actual dose will vary from patient to patient depending *inter alia* on the identity of the peppermint oil, patient body weight, tolerance to the peppermint oil and nature and degree of disorder being treated. It is convenient for each capsule to contain 0.05 ml to 0.5 ml, especially 0.15 ml to 0.35 ml and particularly 0.2 ml to 0.3 ml of the peppermint oil.

The following is a description, by way of example only, of a presently preferred embodiment of the invention.

EXAMPLE

Self-locking hard gelatine capsules (size 2; 0.37 ml) available under the Trade Mark LOK-CAPS were each loaded manually with 0.15 ml Peppermint Oil B.P. dispensed from an automatic pipetting syringe. The filled capsules were placed in a coating tower where they were carried in a heated (55°C) air stream whilst being sprayed with an enteric coating solution. The coating solution had the following composition by weight:–

cellulose acetate phthalate	3%
diethyl phthalate	1%
silicone fluid (200 c.s.)	1%
ethyl acetate	30%
acetone	to100%
Density of solution	870 mg/ml
Solids content	5.5%

An amount of 43.01 ml per 100 capsules was employed to provide a theoretical coating of 6 mg/cm², which is an excess of that theoretically required in order to allow for losses during the coating process.

It will be appreciated that the process described above is a small scale process devised for the purposes of preparing several hundred capsules for clinical evaluation. Production scale processes will almost certainly differ both in terms of the procedure employed and the relative proportions of the coating composition.

Enteric-coated capsules obtained as described above were subjected to the B.P. 1973 disintegration test for enteric-coated tablets (see page A123 British Pharmacopoeia 1973). The capsules were immersed in 0.06N Hydrochloric acid for a 3 hour period and during that time no disintegration took place. However, all the capsules disintegrated within 60 mins. when immersed in a standard solution of pH 6.8.

In order to evaluate *in vivo* disintegration, enterically-coated capsules were prepared as described above but filled with (a) a barium sulphate composition or (b) iodised poppyseed oil. Each of twelve patients chosen at random from patients attending a Barium Meal Clinic were given two of the barium sulphate capsules and two of the iodised poppy-seed oil capsules. The patients were subsequently examined radiologically. The average dissolution time was 143 minutes and the site of dissolution was in the region of the small bowel. The results indicate that the capsules pass intact through the stomach and greater part of the duodenum. Disintegration commenced at the distal end of the duodenum, continuing into the jejunum and finally the casules releases its contents along the length of the ileum.

Thirtytwo patients attending a Colon Clinic showing symptoms consistent with irritable colon syndrome were admitted voluntarily to an open clinical trial. The dose employed was one enteric coated peppermint oil capsule (prepared as described above and containing 0.15 ml Peppermint Oil B.P.) taken three times a day before meals. Clinical assessment of each patient was carried out after an initial treatment period of 14 days. If no side-effects were evident after this period and the patient had benefited from the treatment, it was continued for a further 14 days. After the second 14 day period, the overall patient response to the treatment was documented and comparison made with previous therapy. The treatment was continued indefinitely if beneficial.

Thirteen patients showed excellent response and another twelve showed good response; the remaining seven did not find the treatment beneficial.

Only one patient showed any signs of toxic effects and this took the form of a hypersensitivity reaction to the menthol content of the oil, which reaction disappeared upon terminating the treatment. One other patient suffering from achlorhydria complained of heartburn and burping caused as a result of the capsules disintegrating in the abnormally high pH of the achlorhydric stomach. Some patients who found the treatment beneficial had previously been prescribed diphenoxylate, papaverine, dicyclomine or mebeverine without success.

The results of the test indicated that peppermint oil in enterically coated hard gelatine capsules is an acceptable and effective treatment of irritable colon syndrome.

CLAIMS

1. An enterically coated hard gelatin capsule containing 0.05 ml to 0.5 ml peppermint oil.
2. A capsule as claimed in Claim 1 wherein the coating is a cellulose acetate phthalate coating.
3. A capsule as claimed in either of the preceding Claims wherein the peppermint oil is Peppermint Oil B.P.
4. A capsule as claimed in one of the preceding Claims containing 0.15 to 0.35 ml peppermint oil.
5. A preparation as claimed in Claim 4 containing 0.2 to 0.3 ml peppermint oil.
6. A capsule as claimed in Claim 1 and substantially as hereinbefore described in the Example.

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