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(54) Title: USE OF SIMETHICONE AND SODIUM PICOSULPHATE IN CONSTIPATED PATIENTS SUFFERING FROM
BLOATED FEELING AND GAS DISCOMFORT DURING THE NIGHT

(57) **Abrégé/Abstract:**

The invention relates to the use of simethicone for the preparation of a medication for the treatment of constipated persons suffering from bloated feeling during the night.

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(54) Title: USE OF SIMETHICONE IN CONSTIPATED PATIENTS

(57) Abstract: The invention relates to the use of simethicone for the preparation of a medication for the treatment of constipated persons suffering from bloated feeling during the night.

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25771-1252

**USE OF SIMETHICONE AND SODIUM PICOSULPHATE IN
CONSTIPATED PATIENTS SUFFERING FROM BLOATED FEELING AND
GAS DISCOMFORT DURING THE NIGHT**

5 BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

The invention relates to the use of simethicone for the preparation of a medication for the treatment of constipated persons suffering from bloated feeling.

10 2. BACKGROUND INFORMATION

Constipation is suffered by a considerable number of people. Stomach pressure and bloating is the most suffered accompanying symptom world-wide. Approximately 20% of world wide population suffers from constipation. Some causes are fully known, such as several illnesses and certain medications; other causes are mentioned and broadly accepted, 15 such as food (little fibre intake, not enough liquids and un-regular meals), lifestyle symptoms (stress, little exercise), gender and age.

Dimethicone is a well known pharmaceutical material consisting of linear siloxane polymers containing repeating units of the formula $\{-(CH_2)_2SiO\}_n$ stabilized with 20 trimethylsiloxy end blocking units of the formula $[(CH_3)_3SiO-]$.

Simethicone is the mixture of dimethicone and silicon dioxide. It is well known that simethicone can be used for the relief of flatulence and similar discomforts.

25 Laxative agents include bisacodyl, sodium picosulphate, cascara sagrada, danthron, senna, phenolphthalein, aloe, castor oil, ricinoleic acid, and dehydrocholic acid and mixtures of these laxatives, as well as certain polyethylene glycols (macrogols), lactulose, sorbitol, glycerin, parafine, sodium sulphate and magnesium sulphate, of which bisacodyl, sodium picosulphate and macrogol 3350 are preferred.

30

The French patent application FR 2 828 105 suggests that antifatulents such as simethicone prevent the side effects of poorly absorbed polysaccharides in the treatment or prevention of constipation.

- 5 US patent US 6,676,933 discloses a pharmaceutical composition comprising mosapride, pancreatin and simethicone or dimethicone for the treatment of gastrointestinal disorders such as indigestion, constipation and flatulence.

- 10 The International patent application WO 95/01803 suggests a pharmaceutical composition comprising famotidine for the treatment of gastrointestinal disorders such as indigestion, constipation and optionally simethicone to relieve flatulence.

- The European patent application EP 1 297 825 suggests a composition comprising simethicone and a adsorbant in a ratio of at least 1 : 2.22, furthermore a combination with
15 other active ingredients such as bisacodyl is suggested.

- The product PURGAZEN® of AGEFA GmbH, Austria
(http://aposhop.aponet.at/OTCkatalog/htm/purgazen_dragees.htm) contains a combination of 5 mg bisacodyl and 10 mg of dimeticon.
20

The European patent application EP 1 086 701 A suggests a composition comprising a laxative, in particular bisacodyl or senna; and simethicone for enhancing the efficacy of the laxative.

- 25 There is still a high demand for a medication which allows an immediate effect of reducing the bloated feeling and an overnight relief of constipation in constipated persons.

BRIEF DESCRIPTION OF THE INVENTION

- 30 It has been found surprisingly that simethicone provides an immediate effect on bloated feeling, gas discomfort and flatulence in constipated persons, and that especially the

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combination with bisacodyl achieves an overnight relief of constipation with considerably less flatulence.

Accordingly the invention relates to the use of simethicone for the preparation of a medication for the treatment of constipated persons suffering from bloated feeling during the night.

Moreover, the invention relates to a pharmaceutical composition comprising 80 to 300 mg, in particular 90 to 220 mg, most preferably about 210 mg of simethicone, 2 to 20 mg of bisacodyl and one or more pharmaceutically acceptable carriers and/or auxiliaries, in a way that simethicone reduces the bloated feeling and the flatulence without enhancing the efficacy of bisacodyl against constipation.

A further aspect of the invention is a kit of parts for the preparation of a medication for the treatment of constipated persons suffering from bloated feeling comprising at least two compartments wherein

- (a) one compartment comprises 80 to 300 mg, in particular 90 to 220 mg, most preferably about 210 mg of simethicone and a pharmaceutically acceptable carrier and/or auxiliary,
- (b) the other compartment comprises 2 to 20 mg of bisacodyl and one or more pharmaceutically acceptable carrier and/or auxiliary.

Moreover, the invention relates to a method of treating the bloated feeling of constipated persons during the night, which method comprises administering a therapeutically effective amount of simethicone to said constipated persons.

Moreover, this invention relates to use of simethicone in combination with sodium picosulphate prior to bedtime for reducing bloated feeling and gas discomfort in the treatment of a constipated person suffering from bloated feeling and gas discomfort during the night, while maintaining the efficacy of the sodium picosulphate in the overnight relief of

5 constipation and without premature defecation during the night.

Finally, the invention relates to an article of manufacture comprising packaging material contained within which is the composition effective to treat the bloated feeling of a constipated person according to this invention and the packaging material comprises a label which indicates that the composition can be used to treat the bloated feeling and gas

10 discomfort of a constipated person.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the mean scores of feeling of bloatedness depending on the time after administration until defecation of

- ◆— 10 mg of bisacodyl;
- ▲— 210 mg of simethicone;
- 10 mg of bisacodyl + 210 mg of simethicone.

Figure 2 shows the change from baseline in mean scores of feeling of bloatedness depending on the time after administration until defecation of

- ◆— 10 mg of bisacodyl;
- ▲— 210 mg of simethicone;
- 10 mg of bisacodyl + 210 mg of simethicone.

Figure 3 shows the global assessment of efficacy by patients regarding the feeling of bloatedness after administration of 10 mg of bisacodyl (BS 10mg), 210 mg of simethicone (SM210mg) or 10 mg of bisacodyl + 210 mg of simethicone (BS 10mg + SM210mg)

Figure 4 shows the global assessment of efficacy by patients regarding the constipation after administration of 10 mg of bisacodyl (BS 10mg), 210 mg of simethicone (SM210mg) or 10 mg of bisacodyl + 210 mg of simethicone (BS 10mg + SM210mg).

DETAILED DESCRIPTION OF THE INVENTION

In a preferred embodiment simethicone is used for the treatment of constipated persons, who suffer from bloated feeling during the night.

The level of simethicone in the present invention to reduce bloated feeling in constipated persons is generally from about 80 mg to about 300 mg, preferably from about 90 to about 250 mg, in particular from about 100 mg to about 220 mg, most preferably about 210 mg

per administration. A dosage unit can be one tablet, capsule, or suppository, one teaspoonful of a liquid, or one single portion of any other suitable delivery form.

5 The phrase "constipated person" as used hereinbefore or herein below is intended to mean a person, who suffers from constipation due to illnesses, certain medications; food in-take, lifestyle exercise, gender or age, or any other possible reason. As a rule such a person may be male or female, predominately female, of any age including children, young adults, adults and elder persons, preferably persons in the range of 40 to 80, in particular 45 to 70 years are affected by severe constipation. As a rule the constipated person will not be
10 treated with poorly absorbed polysaccharides.

The phrase "combination therapy" (or "co-therapy"), in defining use of simethicone and a laxative, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects, in particular reduction of the bloated feeling
15 during the night and defecation the following morning, of the drug combination. The phrase also is intended to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent; in this case the simethicone can be taken any time of the day, so that the bloatedness can be treated with immediate effect as it
20 occurs.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in reduction of bloatedness, gas discomfort and relief from constipation of each agent by itself, while
25 avoiding adverse side effects typically associated with alternative therapies.

The phrase "immediate effect" with respect to the reduction of the bloated feeling is intended to mean an effect which sets on within 0 to 6 hours, preferably within 1 to 5 hours, in particular about 2 to 3 hours after administration.
30

The phrase "during the night" or "overnight relief" with respect to the relief of constipation is intended to mean that the defecation takes place 7 to 15 hours, preferably 8 to 14 hours after administration, in particular at the next morning when administered about 0 to 3 hours before bedtime, without any risk of premature defecation.

5

Preferably the complete dose of simethicone, in particular 80 to 300 mg thereof is administered 1 to 5, in particular 2 to 3 hours before said persons go to bed.

Furthermore preferred is a combination therapy, wherein a laxative selected from the group consisting of bisacodyl, sodium picosulphate, and macrogols is co-administered to the constipated person in need thereof.

The level of laxative is the amount necessary to provide the desired effect, which is generally from about 2.0 mg to about 20 mg, preferably from about 2.5 mg to about 15 mg, and most preferably from about 3.0 mg to about 10.0 mg per dose for bisacodyl.

15

Most preferably 2 to 20 mg, in particular 3 to 10 mg of bisacodyl are co-administered in a combined form, or separately or separately and sequentially wherein the sequential administration is close in time.

The ratio of simethicone to bisacodyl in the compositions according to the invention is as a rule in the range of 200 : 1 to 2 : 1, preferably in the range 100 : 1 to 5 : 1, in particular in the range of about 25 : 1 to 15 : 1.

The present invention can be delivered in form of one or more capsules, tablets, a chewable tablets, a liquid drinks, suppositories or other pharmaceutically acceptable forms. Oral delivery forms are preferred.

In a preferred embodiment the invention relates to a pharmaceutical composition comprising two different kinds of granules, one of which is a fast release granule of simethicone and the other is bisacodyl in form of a sustained release granule.

Commonly known pharmaceutically acceptable carriers and/or auxiliaries for orally-administered drugs such as enteric polymers, taste-masking polymers, binders, sweeteners, flavouring agents, dispersants, buffering agents and the like may be included in amounts
5 that do not adversely affect the novel properties of the medication described and claimed herein. Suitable enteric polymer systems include polymethacrylates (e.g. EUDRAGIT L30D or S100, available from Rohm Company); cellulose acetate phthalate; polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate. Suitable binders include microcrystalline cellulose, calcium phosphates, dextrates. Suitable dispersants include
10 croscarmellose sodium, methylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose and the like. Suitable sweeteners include sugar, sorbitol, saccharin, mannitol, glucose, aspartame, sucralose and the like. Flavouring agents include peppermint, spearmint, cinnamon, vanilla and the like. A more complete listing of appropriate additives can be found in numerous publications including
15 Remington's Encyclopedia.

Preferred is a kit of parts which comprises

- (a) one compartment comprising 80 to 300 mg, preferably 80 to 220 mg, most preferably about 210 mg of simethicone in form of a slow release composition,
- 20 (b) one compartment comprising 2 to 20 mg, preferably 3 to 10 mg of bisacodyl in form of a sustained release composition.

EXAMPLES

25 The Examples that follow serve to illustrate some formulations according to the invention. They are intended solely as possible procedures described by way of example, without restricting the invention to their content.

Clinical Studies have been carried out in order to compare the influence of simethicone,
30 bisacodyl and the combined doses of simethicone and bisacodyl on the bloated feeling of constipated persons.

The studies were randomized, open and parallel groups. The studies were designed to assess the safety, tolerability, and preliminary efficacy of simethicone and bisacodyl in patients suffering from constipation.

5

The study was performed with

- simethicone 105 mg per capsule,
- bisacodyl: 5 mg per tablet
- per treatment 2 tablets and/or 2 capsules, respectively
- 10 • patients were asked to take medication approximately 3 hrs before bedtime.

All patients, including male and female aged 45 to 80 years, participated in an outpatient fashion.

- 15 A total of 30 constipated patients, also suffering from bloating participated in these studies.
- 10 patients were administered with 210 mg of simethicone;
 - 10 patients were administered with 10 mg of bisacodyl; and
 - 10 patients were administered with 210 mg of simethicone and 10 mg of bisacodyl.

- 20 Safety assessments included adverse event profile, physical examination, vital sign measurements (defecation, bloating, weight, temperature, heart rate, blood pressure [BP]), clinical laboratory assessments and others.

- 25 All safety analyses were conducted on the safety population, defined as all patients who received at least 1 dose of study medication. Descriptive statistics were provided among other things for vital signs and clinical laboratory assessments.

The results regarding the monitoring of the bloated feeling are shown in Fig. 1 to Fig. 3.

- 30 Fig. 4 additionally shows the results regarding constipation.

The results given in these figures clearly show that the treatment of constipated people with simethicone reduces the bloated feeling relatively fast after ingestion. The laxative effect of bisacodyl combined with the direct effect on the bloated feeling by simethicone results in an immediate effect on the bloated feeling and an overnight relief after ingestion

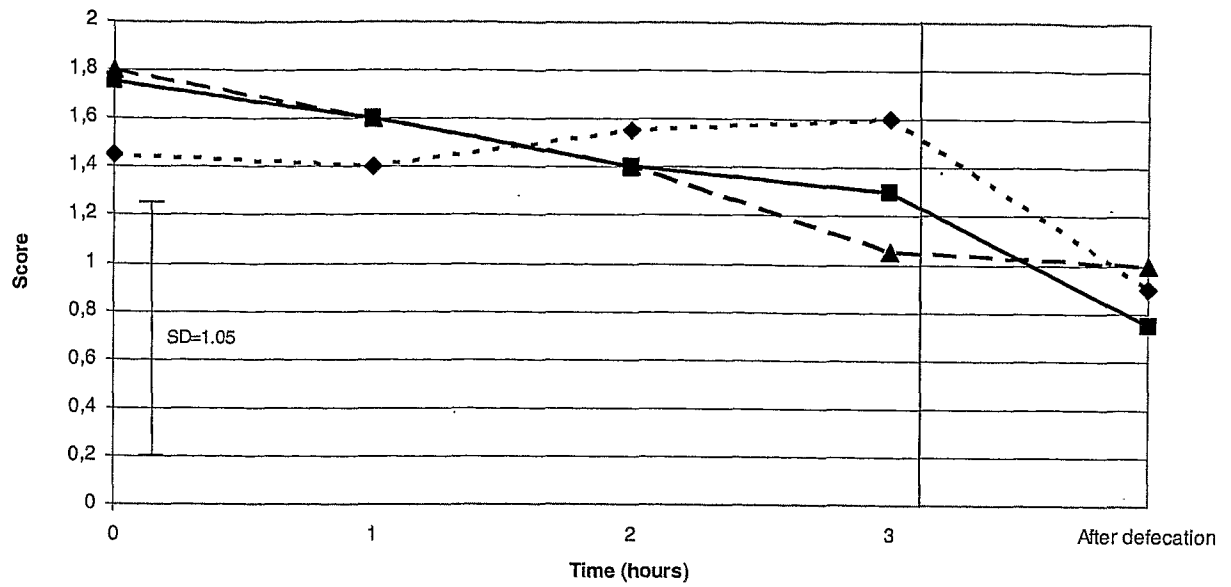
5 in the evening of constipation with considerably less flatulence.

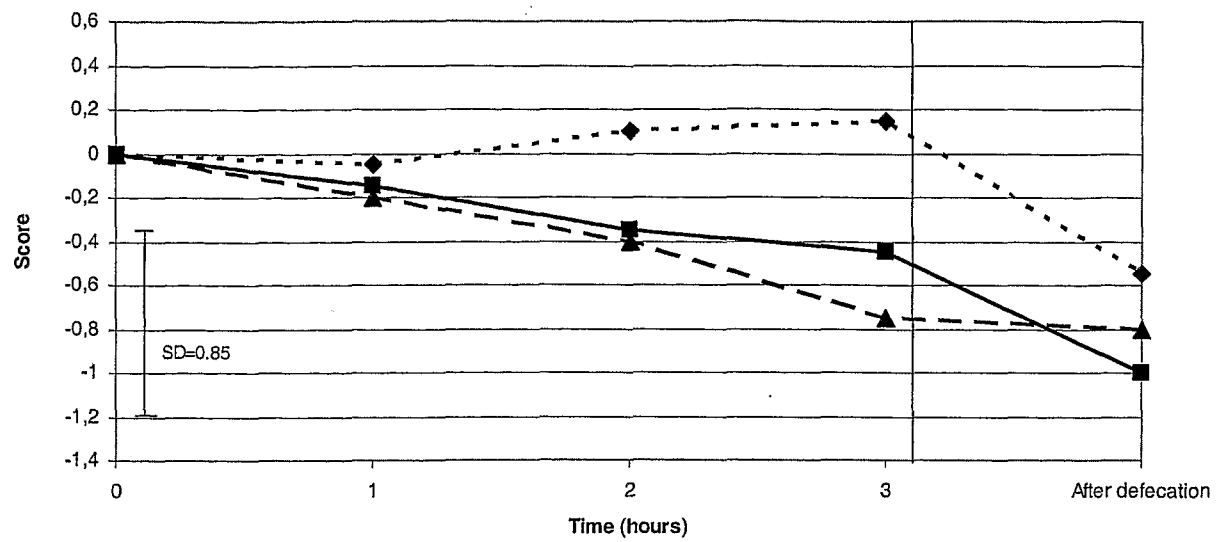
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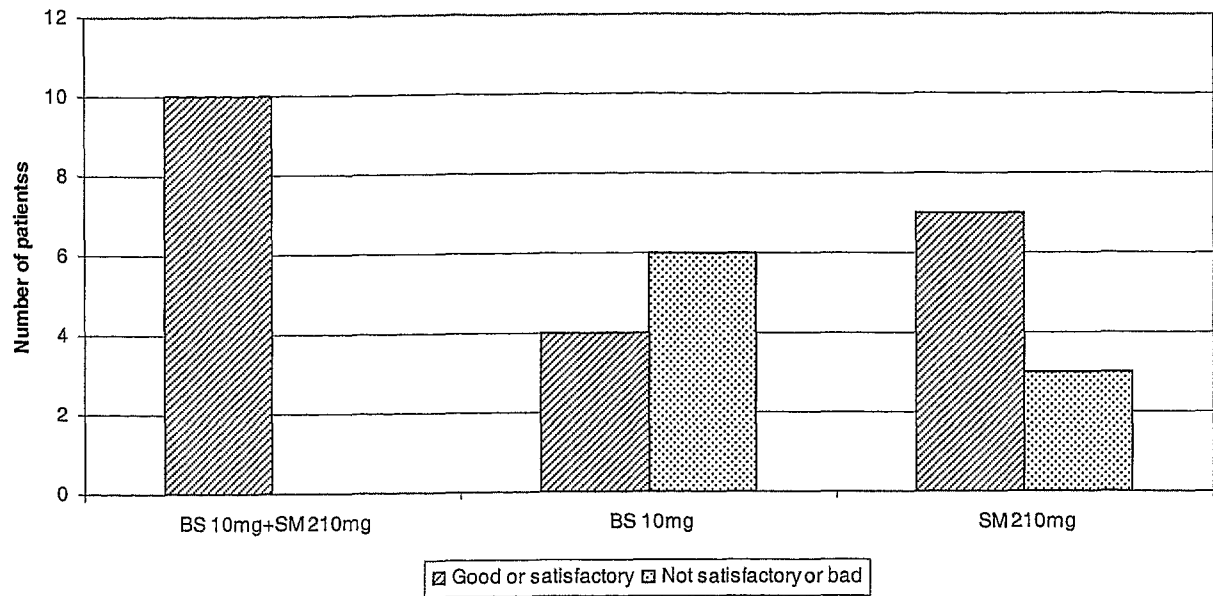
1. Use of simethicone in combination with sodium picosulphate prior to bedtime for reducing bloated feeling and gas discomfort in the treatment of a constipated person suffering from bloated feeling and gas discomfort during the night, while maintaining the efficacy of the sodium picosulphate in the overnight relief of constipation and without premature defecation during the night.
2. Use according to claim 1, comprising a daily dose of simethicone of from 80 to 300 mg.
3. Use according to claim 1 or 2, comprising a daily dose of simethicone of from 90 to 220 mg.
4. Use according to any one of claims 1 to 3, comprising a daily dose of simethicone of from about 210 mg.
5. Use according to any one of claims 1 to 4, wherein the simethicone is for use 1 to 5 hours before bed.
6. Use according to any one of claims 1 to 5, wherein the simethicone is for use about 3 hours before bed.
7. A pharmaceutical composition comprising simethicone and sodium picosulphate for use prior to bedtime for reducing bloated feeling and gas discomfort in the treatment of a constipated person suffering from bloated feeling and gas discomfort during the night, while maintaining the efficacy of the sodium picosulphate in the overnight relief of constipation and without premature defecation during the night.
8. Use of simethicone in combination with sodium picosulphate in the manufacture of a medicament for use prior to bedtime for reducing bloated feeling and gas discomfort in the treatment of a constipated person suffering from bloated feeling and gas

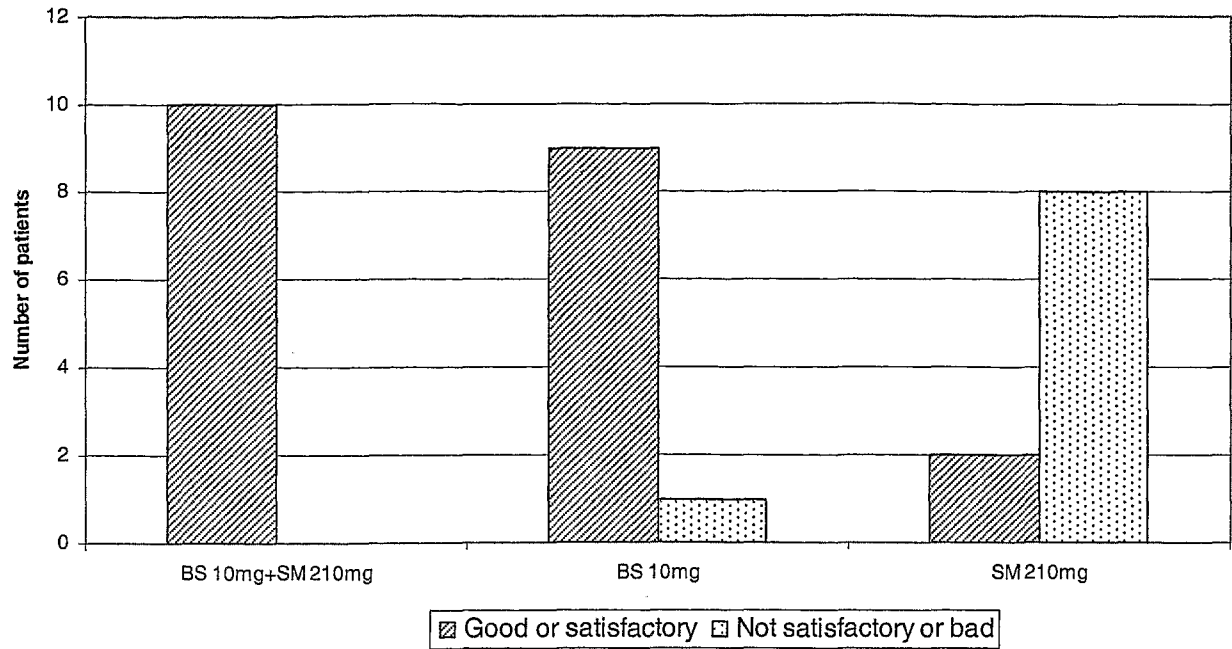
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discomfort during the night, while maintaining the efficacy of the sodium picosulphate in the overnight relief of constipation and without premature defecation during the night.

**Fig. 1**

**Fig. 2**

**Fig. 3**

**Fig. 4**