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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING A PROTON PUMP INHIBITOR AND A PROKINETIC AGENT

(57) Abstract: Oral pharmaceutical compositions and process for preparation thereof are provided comprising at least one gastric acid suppressing agent, preferably a proton pump inhibitor or its pharmaceutically acceptable salts, ester, hydrates, derivatives or prodrugs, and one or more prokinetic agent or its pharmaceutically acceptable salts, esters, hydrates, derivatives or prodrugs, optionally with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and prokinetic agent is present in a bimodal release from such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the proviso that the prokinetic agent is not formulated using a hydrophilic rate controlling polymer and is not present in a sustained release form. Method of treatment of gastro esophageal reflux disease, reflux esophagitis, peptic ulcer, gastric ulcer, and other gastric acid related disorders by administering to a patient such a pharmaceutical composition in need thereof is also provided.



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## PHARMACEUTICAL COMPOSITIONS COMPRISING OF PROTON PUMP INHIBITOR AND PROKINETIC AGENT

### Field of the invention

The present invention relates to pharmaceutical compositions and process for preparing  
5 such compositions comprising of at least one gastric acid suppressing agent and one or  
more prokinetic agent(s) exhibiting a unique bimodal release profile, optionally with  
other pharmaceutically acceptable excipients. Preferably, the present invention  
describes pharmaceutical compositions of a proton pump inhibitor and one or more  
prokinetic agent(s). More preferably, the present invention relates to pharmaceutical  
10 composition of pantoprazole or its pharmaceutically acceptable salts, esters, hydrates,  
or derivatives; and domperidone or its pharmaceutically acceptable salts, esters,  
hydrates, or derivatives. These compositions are especially useful in the treatment of  
gastro-oesophageal reflux disease. Furthermore, the present invention refers to a  
method for the manufacture of such preparations in a way such that there is increased  
15 dissolution of the prokinetic agent at alkaline pH.

### Background of the invention

Gastro esophageal reflux disease (GERD), reflux esophagitis, peptic ulcer, gastric ulcer  
and other gastric acid related disorders are disorders having a pathogenesis related to  
reduced gastric motility and release of excessive gastric acid. Aside from behavioral  
20 changes, GERD and gastric ulcer have been successfully treated with a range of gastric  
acid inhibitors, such as ranitidine and omeprazole, which are acid-suppressing agents.  
Stimulation of gastric motility has been proposed to accelerate the healing of gastric  
ulcer. Prokinetic agents, such as domperidone, are known to enhance gastrointestinal  
motility and prevent duodenogastric reflux, and are widely used to treat GERD. Proton  
25 pump inhibitors and prokinetic agents have been used in combination to treat gastric  
ulcer and other related disorders.

Proton pump inhibitors, such as Lansoprazole, omeprazole, Pantoprazole are rapidly  
taking share from H<sub>2</sub> receptor antagonists, particularly in reflux oesophagitis.

Omeprazole is known to offer significant gain over H<sub>2</sub> receptor antagonists in terms of symptom resolution, healing and prevention of relapse for reflux oesophagitis.

5 A combination therapy of a prokinetic agent and a gastric acid lowering compound is rational and has shown more effectiveness than mono-therapy of proton pump inhibitors. Administration of cisapride and ranitidine was shown to further lower the exposure of the oesophagus to acid(s) (Inauen W et al. Gut 1993; 34: 1025-1031). Such a therapy was also shown to improve healing rates (de Boer WA et al. Aliment Pharmacol Ther 1994; 8: 147-157).

10 Maintenance therapy is often necessary to prevent recurrent symptoms and oesophagitis. A combination therapy combining an acid-suppressing agent with a prokinetic agent has been recently described. [Vyneri et al; N. Engl. J Med 1995; 333: 1106-1110].

15 US patent no. 6,132,771 discloses a combination therapy of proton pump inhibitor and a prokinetic agent wherein, the prokinetic agent may be in the form of instant release, sustained release or extended release formulations. However, prokinetic agents such as domperidone require optimum binding to receptors. Hence, improved therapeutic efficacy may be achieved by administering the drug in timed release form with an initial loading dose and a delayed release dose provided with a lag time.

20 The WO publication no. 95/01803 describes a pharmaceutical composition of famotidine, cisapride and optionally simethicone in the treatment of gastrointestinal distress.

25 The WO publication no. 200471374A2 describes pharmaceutical compositions for once a day oral administration, comprising at least one delayed release component, wherein said delayed release component comprises a proton pump inhibitor, said composition further including at least one immediate release and/or a sustained release prokinetic agent. The said application discloses use of polymers to formulate sustained release compositions of the prokinetic agent. However, such compositions suffer from a major disadvantage in terms of absorption of the prokinetic agent which are primarily

absorbed from the intestine and hence a delayed release composition is highly desirable.

5 Nagarsenker, M. S.; Garad, S. D.; Ramprakash, G. , [Journal of Controlled Release (2000), 63(1-2), 31-39] describe coevaporates of domperidone prepared using different polymers by solvent evaporation technique. The drug release rate was dependent on the concentration of polymers in the coevaporates. Dissolution of drug in a pH 6.8 buffer improved with increasing concentration of hydroxypropyl methyl cellulose phthalate in coevaporates.

10 However, there still exist a need to develop pharmaceutical compositions comprising a combination of a gastric acid suppressing agent preferably a proton pump inhibitor and a prokinetic agent wherein the prokinetic agent is present in an immediate release form and a delayed release form useful for the treatment of gastro esophageal reflux disease, reflux esophagitis, peptic ulcer, gastric ulcer, and other gastric acid related disorders. The delayed release form of the prokinetic agent is highly essential since most of the  
15 prokinetic agents show a better absorption generally from the intestinal region of the GIT, which is an objective of the present invention.

#### Summary of the invention

It is an objective of the present invention to provide an oral pharmaceutical composition comprising at least one gastric acid suppressing agent and one or more  
20 prokinetic agent, optionally with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is present in a bimodal release form such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the proviso that the prokinetic agent is not formulated using  
25 a rate controlling polymer and is not present in a sustained release form.

It is an objective of the present invention to provide oral pharmaceutical composition comprising a proton pump inhibitor, preferably pantoprazole or its pharmaceutically acceptable salts, esters, hydrates, derivatives or prodrugs, and domperidone or its  
30 pharmaceutically acceptable salts, esters, hydrates, or derivatives thereof.

It is also an objective of the present invention to provide a process for preparing a composition comprising at least one gastric acid suppressing agent and one or more prokinetic agent, optionally with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is present in a bimodal release form such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the proviso that the prokinetic agent is not formulated using a rate controlling polymer and is not present in a sustained release form, which comprises of the following steps:

- 10     i)     processing the acid suppressing agent with pharmaceutically acceptable excipients
- ii)    processing the prokinetic agent with pharmaceutically acceptable excipients
- iii)   formulating the material of step i) and ii) into a suitable dosage form.

15    It is yet another objective to provide a method of treatment of gastro esophageal reflux disease, reflux esophagitis, peptic ulcer, gastric ulcer, and other gastric acid related disorders by administering to a patient in need thereof a pharmaceutical composition of the present invention.

#### **Detailed description of invention**

20    A combination therapy comprising a gastric acid suppressing agent and a prokinetic agent is attractive, rational and effective. A combination of gastric acid suppressing agent and prokinetic agent could be an alternative to each of them separately in case of failure. However, because of the large number of therapeutical tablets/pills that must be taken each day in such a therapy, the compliance of such a treatment may be a problem.

25    It is well known that patient compliance is a major factor in receiving good results in medical treatments. Administration of two, three or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more different active substances combined in one fixed unit dosage form, preferably tablets in a capsule.

30    The present invention relates to pharmaceutical compositions comprising of at least one gastric acid suppressing agent and one or more prokinetic agent(s) optionally with other

pharmaceutically acceptable excipients. Preferably, the present invention describes pharmaceutical compositions of a proton pump inhibitor and one or more prokinetic agent(s). More preferably, the present invention relates to pharmaceutical composition of pantoprazole or its pharmaceutically acceptable salts, esters, hydrates, derivatives or  
5 prodrugs; and domperidone or its pharmaceutically acceptable salts, esters, hydrates, derivatives or prodrugs.

One aspect of the present invention relates to oral pharmaceutical compositions of gastric motility modifying agents and their combination therapies wherein the gastric motility-modifying agent has a unique bimodal release profile. The prokinetic agent is  
10 present in a bimodal release form such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the proviso that the prokinetic agent is not formulated using a rate controlling polymer and is not present in a sustained release form. These preparations are especially useful in the treatment of gastro-oesophageal reflux disease.

15 The proton pump inhibitor of the present invention is selected from but not limited to a group comprising pantoprazole, lansoprazole, omeprazole, esomeprazole, rabeprazole, and the like, their pharmaceutically acceptable salts, esters, hydrates, derivatives or prodrugs, used either alone or in combination thereof.

20 The prokinetic agent of the present invention is selected from but not limited to a group comprising domperidone, metoclopramide, itopride, mosapride, cisapride, renzapride, zacopride, octreotide, naloxone, erythromycin and bethanechol, Motilides such as Motilin, and the like, their pharmaceutically acceptable salts, esters, hydrates, derivatives or prodrugs, used either alone or in combination thereof. Preferably the  
25 prokinetic agent is domperidone, or metoclopramide, or pharmaceutically acceptable salts, esters, hydrates, or derivatives thereof.

The other pharmaceutically acceptable excipients of the present invention are selected from but not limited to the group comprising of diluents, binders, disintegrants, colorants, lubricants, plasticizers, coating agents, opacifiers, antioxidants, and the like  
30 used either alone or in combination thereof.

Suitable diluents according to the present invention are selected from but not limited to a group comprising microcrystalline cellulose such as Avicel® PH 101, Avicel® PH 102, Avicel® PH 112, Avicel® PH 200, Avicel® PH301 and Avicel® PH 302, lactose such as lactose monohydrate, lactose anhydrous and Pharmatose® DCL21, dibasic calcium phosphate, saccharides such as mannitol, Pearlitol® SD 200, starch, sorbitol, sucrose, and glucose; alkaline agents such as magnesium oxide, sodium bicarbonate, or mixtures thereof.

Suitable disintegrants according to the present invention are selected from but not limited to a group comprising crosslinked polyvinyl pyrrolidone, polyvinyl pyrrolidone, corn starch, potato starch, maize starch and modified starches, croscarmellose sodium, sodium starch glycolate, low substituted hydroxypropyl cellulose, or mixtures thereof.

Suitable lubricants according to the present invention are selected from but not limited to colloidal silicon dioxide, talc, stearic acid, magnesium stearate, calcium stearate, zinc stearate, and sodium stearyl fumarate, or mixtures thereof.

Suitable coating materials according to the present invention are selected from but not limited to Hydroxypropyl methylcellulose, Eudragit L-100, Eudragit L-100 55, Opadry® yellow 03B52544 (Colorcon), Opadry® white OY-IN-58901 (Colorcon), Opadry® pink 03B54579 (Colorcon), Triethyl citrate, propylene glycol, colloidal silicon dioxide, Talc, Isopropyl alcohol, Dichloromethane, purified water, and the like.

During developmental studies of the present invention, it was surprisingly found that when domperidone was co-processed with an organic acid it exhibited an improved dissolution even at alkaline pH conditions encountered in the gastro-intestinal tract.

According to a preferred embodiment of the invention, domperidone is co-processed with an organic acid in the ratio of from about 1:0.25 to about 0.25:1, preferably from about 1:0.5 to about 0.5:1, most preferably about 1:1. The co-processing may be aided by dissolving the two ingredients with the help of heat followed by cooling, when the dissolved material separates out. The material separated out may be removed and dried. The co-processed material may be incorporated into dosage forms such as tablets,

which may further be combined with enteric coated tablets of proton pump inhibitor and an immediate release tablet of domperidone, in a hard gelatin capsule.

5 In yet another embodiment, the composition comprises the prokinetic agent as 5 to 70 % by weight of total prokinetic agent in immediate release form and the remaining prokinetic agent in delayed release form.

10 In another embodiment of the present invention, the composition of the prokinetic agent present in immediate release form and delayed release form comprises a permeation enhancer, preferably Vitamin E tocopheryl propylene glycol succinate

15 In an embodiment, the composition of the present invention is in the form of a multiparticulate composition comprising a blend of one or more types of particles, pellets or mini-tablets having different release characteristics, optionally filled into a capsule; or a tablet, or formulated as a liquid dosage form.

The present invention provides oral dosage forms, such as multiple unit tableted dosage form, or a capsule filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible proton pump inhibitor which is protected by an enteric coating layer, and one or more  
20 prokinetic agents. The prokinetic agent is preferably incorporated as a better dissolving complex with bimodal release. These new compositions intend to simplify the regimen and improve the patient compliance.

25 In a preferred embodiment of the present invention, the composition is in the form of tablets filled into hard gelatin capsule, or in the form of multilayer tablets.

In another embodiment, a process for preparing a composition is provided comprising at least one gastric acid suppressing agent and one or more prokinetic agent, optionally with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is  
30 present in a bimodal release form such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with

the proviso that the prokinetic agent is not present in a sustained release form, which comprises of the following steps:

- i) processing the acid suppressing agent with pharmaceutically acceptable excipients into enteric coated tablets
- 5 ii) processing the prokinetic agent with pharmaceutically acceptable excipients partly into film coated tablets and partly into enteric coated tablets
- iii) filling one enteric coated tablet comprising an acid suppressing agent, and one film coated tablet and one enteric coated tablet comprising a prokinetic agent, into a hard gelatin capsule.
- 10 In a further embodiment, the process for preparing a composition is provided comprising at least one gastric acid suppressing agent and one or more prokinetic agent, optionally with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is present in a bimodal release form such as an immediate release form to provide
- 15 an initial loading dose, and a delayed release form to provide a dose with a lag time; with the proviso that the prokinetic agent is not present in a sustained release form, which comprises of the following steps:
  - i) processing the acid suppressing agent with pharmaceutically acceptable excipients into enteric coated granules
  - 20 ii) processing one part of the prokinetic agent with pharmaceutically acceptable excipients into immediate release granules, and the other part into enteric coated granules
  - iii) compressing the granules of step i) and ii) into a multilayer tablet
  - iv) optionally coating the tablet
- 25 The examples given below serve to illustrate embodiments of the present invention. However, they do not intend to limit the scope of the present invention.

**Example 1: Pantoprazole and Domperidone Tablets in a Capsule**

**Part A: Pantoprazole Tablets (Delayed release)**

| <b>Ingredients</b>                | <b>Quantity<br/>mg/Tablet</b> |
|-----------------------------------|-------------------------------|
| Pantoprazole sodium sesquihydrate | 45.10                         |
| equivalent to Pantoprazole 40 mg  |                               |

|                              |       |
|------------------------------|-------|
| Sodium carbonate (anhydrous) | 10.00 |
| Microcrystalline cellulose   | 20.90 |
| Croscarmellose sodium        | 20.00 |
| Magnesium stearate           | 2.00  |
| Talc                         | 2.00  |

**SEAL COATING FORMULA**

|                         |      |
|-------------------------|------|
| Opadry® yellow 03B52544 | 2.0  |
| Isopropyl alcohol       | q.s. |
| Dichloromethane         | q.s. |

**ENTERIC COATING FORMULA**

|                   |      |
|-------------------|------|
| Eudragit® L-100   | 10.0 |
| Triethyl citrate  | 2.0  |
| Talc              | 1.0  |
| Isopropyl alcohol | q.s. |
| Dichloromethane   | q.s. |

**Part B: Domperidone film coated tablets (Immediate release)**

| <b>Ingredients</b>                              | <b>Quantity<br/>mg/Tablet</b> |
|-------------------------------------------------|-------------------------------|
| Domperidone                                     | 10.0                          |
| Citric acid                                     | 20.0                          |
| Vitamin E tocopheryl propylene glycol succinate | 1.0                           |
| Lactose                                         | 45.0                          |
| Croscarmellose sodium                           | 10.0                          |
| Purified water                                  | q.s.                          |
| Magnesium stearate                              | 2.0                           |
| Talc                                            | 2.0                           |

**COATING FORMULA**

|                           |      |
|---------------------------|------|
| Opadry® white OY-IN-58901 | 2.0  |
| Isopropyl alcohol         | q.s. |
| Dichloromethane           | q.s. |

**Part C: Domperidone enteric coated tablets (Delayed release)**

| <b>Ingredients</b>                              | <b>Quantity<br/>mg/Tablet</b> |
|-------------------------------------------------|-------------------------------|
| Domperidone                                     | 10.0                          |
| Citric acid                                     | 20.0                          |
| Vitamin E tocopheryl propylene glycol succinate | 1.0                           |
| Lactose                                         | 45.0                          |
| Croscarmellose sodium                           | 10.0                          |
| Purified water                                  | q.s.                          |
| Magnesium stearate                              | 2.0                           |
| Talc                                            | 2.0                           |

**COATING FORMULA**

|                       |      |
|-----------------------|------|
| Opadry® pink 03B54519 | 2.0  |
| Isopropyl alcohol     | q.s. |
| Dichloromethane       | q.s. |

**ENTERIC COATING FORMULA**

|                   |      |
|-------------------|------|
| Eudragit® L-100   | 8.0  |
| Triethyl citrate  | 2.0  |
| Talc              | 1.0  |
| Isopropyl alcohol | q.s. |
| Dichloromethane   | q.s. |

## Procedure:

**Pantoprazole Tablets**

1. Slug/deslug Pantoprazole, Anhydrous Sodium carbonate, Magnesium stearate and Talc mixture.
- 5 2. Mix extra granular material, Microcrystalline cellulose & Croscarmellose sodium and lubricate with Magnesium stearate and Talc and compress into tablets.
3. Coat the tablets with Opadry® Yellow 03B52544 and then with Eudragit® L-100.

10 **Domperidone Tablets**

4. Dissolve citric acid in hot water. Add Domperidone and Vitamin E TPGS to this hot solution. Stir the slurry for 3-4 hours and allow to cool. Then filter the slurry, dry the residue, and mill to required mesh size.
5. Add Lactose and Croscarmellose sodium, Magnesium stearate and Talc and  
15 compress into tablets.
6. Coat half of the tablets with Opadry® white OY-IN-58901.
7. The remaining tablets of step 3 were coated with Opadry® pink 03B54519 and then with Eudragit® L 100.
8. Fill one Pantoprazole tablet, one enteric coated Domperidone tablet and one  
20 film coated Domperidone tablet into each hard gelatin capsule.

The Dissolution of the capsule formulated above is carried out using USP Dissolution apparatus Type-2 (paddle) at 100 RPM as follows:

Acid stage: Dissolution medium: 0.1M HCL, 750 ml; Time: 2 hours

Buffer stage: Dissolution medium: Phosphate buffer 6.8 USP, 1000 ml; Time: 1 hour

- 25 The dissolution profile of Pantoprazole and Domperidone is given below in tables 1 and 2; and is shown in figures 1 and 2 respectively.

Table 1: Dissolution profile of Pantoprazole enteric coated tablet

| Dissolution condition                  | Time (mins.) | % drug released |
|----------------------------------------|--------------|-----------------|
|                                        | 0            | 0               |
| Acid stage (0.1 N HCl)                 | 120          | 0.14            |
| Buffer Stage (pH 6.8 phosphate buffer) | 135          | 45.72           |
|                                        | 150          | 101.67          |
|                                        | 165          | 101.72          |

Table 2: Dissolution profile of Domperidone enteric coated tablet

| Dissolution condition                  | Time (mins.) | % drug released |
|----------------------------------------|--------------|-----------------|
| Acid stage (0.1 N HCl)                 | 0            | 0               |
|                                        | 45           | 48.64           |
|                                        | 120          | 50.12           |
| Buffer Stage (pH 6.8 phosphate buffer) | 135          | 57.57           |
|                                        | 150          | 89.97           |
|                                        | 165          | 96.01           |

## 5 Example 2: Pantoprazole and Metoclopramide Tablets in a Capsule

### Part A: Pantoprazole Tablets (Delayed release)

| Ingredients                                                           | Quantity<br>mg/Tablet |
|-----------------------------------------------------------------------|-----------------------|
| Pantoprazole sodium sesquihydrate<br>equivalent to Pantoprazole 40 mg | 45.10                 |
| Sodium carbonate (anhydrous)                                          | 12.00                 |
| Mannitol                                                              | 5.00                  |
| Microcrystalline cellulose                                            | 5.90                  |
| Crospovidone                                                          | 15.00                 |
| Calcium stearate                                                      | 1.00                  |
| Talc                                                                  | 1.00                  |

**SEAL COATING FORMULA**

|                         |      |
|-------------------------|------|
| Opadry® yellow 03B52544 | 2.0  |
| Isopropyl alcohol       | q.s. |
| Dichloromethane         | q.s. |

**ENTERIC COATING FORMULA**

|                    |      |
|--------------------|------|
| Eudragit® L-100 55 | 10.0 |
| Triethyl citrate   | 2.0  |
| Talc               | 1.0  |
| Isopropyl alcohol  | q.s. |
| Dichloromethane    | q.s. |

**Part B: Metoclopramide film coated tablets (Immediate release)**

| <b>Ingredients</b>    | <b>Quantity<br/>mg/Tablet</b> |
|-----------------------|-------------------------------|
| Metoclopramide        | 10.0                          |
| Lactose               | 45.0                          |
| Croscarmellose sodium | 10.0                          |
| Magnesium stearate    | 2.0                           |
| Talc                  | 2.0                           |

**COATING FORMULA**

|                           |      |
|---------------------------|------|
| Opadry® white OY-IN-58901 | 2.0  |
| Isopropyl alcohol         | q.s. |
| Dichloromethane           | q.s. |

**Part C: Metoclopramide enteric coated tablets (Delayed release)**

| <b>Ingredients</b>    | <b>Quantity<br/>mg/Tablet</b> |
|-----------------------|-------------------------------|
| Metoclopramide        | 20.0                          |
| Lactose               | 45.0                          |
| Croscarmellose sodium | 10.0                          |

|                    |     |
|--------------------|-----|
| Magnesium stearate | 2.0 |
| Talc               | 2.0 |

**COATING FORMULA**

|                       |      |
|-----------------------|------|
| Opadry® pink 03B54519 | 2.0  |
| Isopropyl alcohol     | q.s. |
| Dichloromethane       | q.s. |

**ENTERIC COATING FORMULA**

|                    |      |
|--------------------|------|
| Eudragit® L-100 55 | 8.0  |
| Triethyl citrate   | 2.0  |
| Talc               | 1.0  |
| Isopropyl alcohol  | q.s. |
| Dichloromethane    | q.s. |

Procedure:

**Pantoprazole Tablets**

1. Slug/deslug Pantoprazole, Anhydrous Sodium carbonate, Calcium stearate and  
5 Talc mixture.
2. Mix extra-granular material, mannitol, microcrystalline cellulose & Kollidon CL and lubricate with calcium stearate and Talc and compress into tablets.
3. Coat the tablets with Opadry Yellow and then with Eudragit L-100 55.

**10 Metoclopramide Tablets**

4. Mix Metoclopramide, Lactose and Croscarmellose sodium, Magnesium stearate and Talc and compress into tablets.
5. Coat half of the tablets with Opadry white.
6. The remaining tablets of step 3 were coated with Opadry pink and then with  
15 Eudragit L-100 55.
7. Fill one Pantoprazole tablet, one enteric coated Metoclopramide tablet and one film coated Metoclopramide tablet into each hard gelatin capsule.

**Example 3: Rabeprazole and Itopride Tablets in a Capsule****Part A: Rabeprazole Tablets (Delayed release)**

| <b>Ingredients</b>          | <b>Quantity<br/>mg/capsule</b> |
|-----------------------------|--------------------------------|
| Rabeprazole sodium          | 20.00                          |
| Magnesium oxide (anhydrous) | 80.00                          |
| Mannitol                    | 5.00                           |
| Microcrystalline cellulose  | 5.90                           |
| Crospovidone                | 15.00                          |
| Calcium stearate            | 1.00                           |
| Talc                        | 1.00                           |

**SEAL COATING FORMULA**

|                         |      |
|-------------------------|------|
| Opadry® yellow 03B52544 | 2.0  |
| Isopropyl alcohol       | q.s. |
| Dichloromethane         | q.s. |

**ENTERIC COATING FORMULA**

|                    |      |
|--------------------|------|
| Eudragit® L-100 55 | 10.0 |
| Triethyl citrate   | 2.0  |
| Talc               | 1.0  |
| Isopropyl alcohol  | q.s. |
| Dichloromethane    | q.s. |

**5 Part B: Itopride film coated tablets (Immediate release)**

| <b>Ingredients</b>    | <b>Quantity<br/>mg/Tablet</b> |
|-----------------------|-------------------------------|
| Itopride              | 50.0                          |
| Lactose               | 45.0                          |
| Croscarmellose sodium | 10.0                          |
| Magnesium stearate    | 2.0                           |

|      |     |
|------|-----|
| Talc | 2.0 |
|------|-----|

**COATING FORMULA**

|                           |      |
|---------------------------|------|
| Opadry® white OY-IN-58901 | 2.0  |
| Isopropyl alcohol         | q.s. |
| Dichloromethane           | q.s. |

**Part C: Itopride enteric coated tablets (Delayed release)**

| <b>Ingredients</b>    | <b>Quantity<br/>mg/Tablet</b> |
|-----------------------|-------------------------------|
| Itopride              | 100.0                         |
| Lactose               | 45.0                          |
| Croscarmellose sodium | 10.0                          |
| Magnesium stearate    | 2.0                           |
| Talc                  | 2.0                           |

**COATING FORMULA**

|                       |      |
|-----------------------|------|
| Opadry® pink 03B54519 | 2.0  |
| Isopropyl alcohol     | q.s. |
| Dichloromethane       | q.s. |

**ENTERIC COATING FORMULA**

|                    |      |
|--------------------|------|
| Eudragit® L-100 55 | 8.0  |
| Triethyl citrate   | 2.0  |
| Talc               | 1.0  |
| Isopropyl alcohol  | q.s. |
| Dichloromethane    | q.s. |

Procedure:

**5 Rabeprazole Tablets**

1. Slug/deslug Rabeprazole, Magnesium oxide, Calcium stearate and Talc mixture.
2. Mix extra-granular material, mannitol, microcrystalline cellulose & Kollidon CL and lubricate with calcium stearate and Talc and compress into tablets.

3. Coat the tablets with Opadry Yellow and then with Eudragit L-100 55.

#### **Itopride Tablets**

4. Mix Itopride, Lactose and Croscarmellose sodium, Magnesium stearate and Talc and compress into tablets.
5. Coat half of the tablets with Opadry white.
6. The remaining tablets of step 3 were coated with Opadry pink and then with Eudragit L-100 55.
7. Fill one Rabeprazole tablet, one enteric coated Itopride tablet and one film coated Itopride tablet into each hard gelatin capsule.

10

#### **Example 4: Omeprazole and Domperidone Tablets in a Capsule**

##### **Part A: Omeprazole Tablets (Delayed release)**

| <b>Ingredients</b>           | <b>Quantity<br/>mg/Tablet</b> |
|------------------------------|-------------------------------|
| Omeprazole                   | 40.00                         |
| Sodium carbonate (anhydrous) | 10.00                         |
| Microcrystalline cellulose   | 20.90                         |
| Croscarmellose sodium        | 20.00                         |
| Magnesium stearate           | 2.00                          |
| Talc                         | 2.00                          |

##### **SEAL COATING FORMULA**

|                         |      |
|-------------------------|------|
| Opadry® yellow 03B52544 | 2.0  |
| Isopropyl alcohol       | q.s. |
| Dichloromethane         | q.s. |

##### **ENTERIC COATING FORMULA**

|                   |      |
|-------------------|------|
| Eudragit® L-100   | 10.0 |
| Triethyl citrate  | 2.0  |
| Talc              | 1.0  |
| Isopropyl alcohol | q.s. |
| Dichloromethane   | q.s. |

**Part B: Domperidone film coated tablets (Immediate release)**

| <b>Ingredients</b>                              | <b>Quantity<br/>mg/Tablet</b> |
|-------------------------------------------------|-------------------------------|
| Domperidone                                     | 10.0                          |
| Citric acid                                     | 20.0                          |
| Vitamin E tocopheryl propylene glycol succinate | 1.0                           |
| Lactose                                         | 45.0                          |
| Croscarmellose sodium                           | 10.0                          |
| Purified water                                  | q.s.                          |
| Magnesium stearate                              | 2.0                           |
| Talc                                            | 2.0                           |

**COATING FORMULA**

|                           |      |
|---------------------------|------|
| Opadry® white OY-IN-58901 | 2.0  |
| Isopropyl alcohol         | q.s. |
| Dichloromethane           | q.s. |

**Part C: Domperidone enteric coated tablets (Delayed release)**

| <b>Ingredients</b>                              | <b>Quantity<br/>mg/Tablet</b> |
|-------------------------------------------------|-------------------------------|
| Domperidone                                     | 10.0                          |
| Citric acid                                     | 20.0                          |
| Vitamin E tocopheryl propylene glycol succinate | 1.0                           |
| Lactose                                         | 45.0                          |
| Croscarmellose sodium                           | 10.0                          |
| Purified water                                  | q.s.                          |
| Magnesium stearate                              | 2.0                           |
| Talc                                            | 2.0                           |

**COATING FORMULA**

|                       |     |
|-----------------------|-----|
| Opadry® pink 03B54519 | 2.0 |
|-----------------------|-----|

|                   |      |
|-------------------|------|
| Isopropyl alcohol | q.s. |
| Dichloromethane   | q.s. |

**ENTERIC COATING FORMULA**

|                   |      |
|-------------------|------|
| Eudragit® L-100   | 8.0  |
| Triethyl citrate  | 2.0  |
| Talc              | 1.0  |
| Isopropyl alcohol | q.s. |
| Dichloromethane   | q.s. |

Procedure:

**Omeprazole Tablets**

1. Slug/deslug Omeprazole, Anhydrous Sodium carbonate, Magnesium stearate and Talc mixture.
2. Mix extra granular material, Microcrystalline cellulose & Croscarmellose sodium and lubricate with Magnesium stearate and Talc and compress into tablets.
3. Coat the tablets with Opadry Yellow and then with Eudragit L-100.

**Domperidone Tablets**

4. Dissolve citric acid in hot water. Add Domperidone and Vitamin E TPGS to this hot solution. Stir the slurry for 3-4 hours and allow to cool. Then filter the slurry, dry the residue, and mill to required mesh size.
5. Add Lactose and Croscarmellose sodium, Magnesium stearate and Talc and compress into tablets.
6. Coat half of the tablets with Opadry white.
7. The remaining tablets of step 3 were coated with Opadry pink and then with Eudragit L 100.

Fill one Pantoprazole tablet, one enteric coated Domperidone tablet and one film coated Domperidone tablet into each hard gelatin capsule.

## CLAIMS

1. An oral pharmaceutical composition comprising at least one gastric acid suppressing agent and one or more prokinetic agent, optionally with other  
5 pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is present in a bimodal release form such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the proviso that the prokinetic agent is not formulated  
10 using a rate controlling polymer and is not present in a sustained release form.
2. A composition according to claim 1, wherein the gastric acid suppressing agent is a proton pump inhibitor.
3. A composition according to claim 2, wherein the proton pump inhibitor is selected from a group comprising pantoprazole, lansoprazole, omeprazole,  
15 esomeprazole, rabeprazole, their pharmaceutically acceptable salts, esters, hydrates, or derivatives, used either alone or in combination thereof.
4. A composition according to claim 3, wherein the proton pump inhibitor is pantoprazole, or its pharmaceutically acceptable salts, esters, hydrates, derivatives or prodrugs thereof.
- 20 5. A composition according to claim 1, wherein the prokinetic agent is selected from a group comprising domperidone, metoclopramide, itopride, cisapride, renzapride, zacopride, octreotide, naloxone, erythromycin and bethanechol, Motilides such as Motilin, their pharmaceutically acceptable salts, esters, hydrates, or derivatives, used either alone or in combination thereof.
- 25 6. A composition according to claim 5, wherein the prokinetic agent is domperidone, or its pharmaceutically acceptable salts, esters, hydrates, derivatives or prodrugs thereof.
7. A composition according to claim 5, wherein the prokinetic agent is metoclopramide, or pharmaceutically acceptable salts, esters, hydrates,  
30 derivatives or prodrugs thereof.
8. A composition according to any of the preceding claims, wherein the prokinetic agent is co-processed with an organic acid.

9. A composition according to any of the preceding claims, wherein the other pharmaceutically acceptable excipients are selected from the group comprising of diluents, binders, disintegrants, colorants, lubricants, plasticizers, coating agents, opacifiers, antioxidants, and the like used either alone or in combination thereof.
10. A composition according to claim 1, which is in the form of tablets filled into hard gelatin capsule.
11. A composition according to claim 1, which is in the form of multilayer tablets.
12. A composition according to claims 1-11, wherein the one prokinetic agent present in the immediate release form and delayed release form is the same.
13. A composition according to claim 8, wherein the ratio of prokinetic agent to the organic acid is from 1:0.25 to about 0.25:1.
14. A composition according to claim 8, wherein the ratio of prokinetic agent to the organic acid is from 1:0.5 to about 0.5:1.
15. A composition according to claim 8, wherein the ratio of prokinetic agent to the organic acid is 1:1.
16. A composition as claimed in any of the preceding claims wherein the prokinetic agent is present as 5 to 70 % by weight of total prokinetic agent in immediate release form and the remaining prokinetic agent in delayed release form.
17. A composition as claimed in any of the preceding claims wherein the prokinetic agent present in immediate release form and delayed release form comprises a permeation enhancer.
18. A composition as claimed in claim 17, wherein the permeation enhancer is Vitamin E tocopheryl propylene glycol succinate.
19. A process for preparing a composition according to claim 1 comprising at least one gastric acid suppressing agent and one or more prokinetic agent, optionally with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is present in a bimodal release form such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the proviso that the prokinetic agent is not

formulated using a hydrophilic rate controlling polymer and is not present in a sustained release form, which comprises of the steps:

- i) processing the acid suppressing agent with pharmaceutically acceptable excipients
- 5 ii) processing the prokinetic agent with pharmaceutically acceptable excipients
- iii) formulating the material of step i) and ii) into a suitable dosage form.

20. A process for preparing a composition according to claim 19 comprising at least one gastric acid suppressing agent and one or more prokinetic agent, optionally  
10 with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is present in a bimodal release form such as an immediate release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the provisio that the prokinetic agent is not  
15 formulated using a rate controlling polymer and is not present in a sustained release form, which comprises of the following steps:

- i) processing the acid suppressing agent with pharmaceutically acceptable excipients into enteric coated tablets
- 20 ii) processing the prokinetic agent with pharmaceutically acceptable excipients partly into film coated tablets and partly into enteric coated tablets
- iii) filling one enteric coated tablet comprising an acid suppressing agent, and one film coated tablet and one enteric coated tablet comprising a prokinetic agent, into a hard gelatin capsule.

25 21. A process for preparing a composition according to claim 19 comprising at least one gastric acid suppressing agent and one or more prokinetic agent, optionally with other pharmaceutically acceptable excipients, characterized in that the gastric acid suppressing agent is present in a delayed release form and the prokinetic agent is present in a bimodal release form such as an immediate  
30 release form to provide an initial loading dose, and a delayed release form to provide a dose with a lag time; with the provisio that the prokinetic agent is not formulated using a rate controlling polymer and is not present in a sustained release form, which comprises of the following steps:

- i) processing the acid suppressing agent with pharmaceutically acceptable excipients into enteric coated granules
  - ii) processing one part of the prokinetic agent with pharmaceutically acceptable excipients into immediate release granules, and the other part  
5 into enteric coated granules
  - iii) compressing the granules of step i) and ii) into a multilayer tablet
  - iv) Optionally coating the tablet
22. A process for preparing a composition according to claim 19-21, wherein  
wherein the gastric acid suppressing agent is a proton pump inhibitor.
- 10 23. A composition according to claims 19-22, wherein the proton pump inhibitor is  
selected from a group comprising pantoprazole, lansoprazole, omeprazole,  
esomeprazole, rabeprazole, their pharmaceutically acceptable salts, esters,  
hydrates, or derivatives, used either alone or in combination thereof.
24. A process for preparing a composition according to claims 19-23, wherein the  
15 proton pump inhibitor is pantoprazole, or its pharmaceutically acceptable salts,  
esters, hydrates, or derivatives thereof.
25. A process for preparing a composition according to claim 19-23, wherein the  
prokinetic agent is selected from a group comprising domperidone,  
metoclopramide, itopride, cisapride, renzapride, zacopride, octreotide,  
20 naloxone, erythromycin and bethanechol, Motilides such as Motilin, their  
pharmaceutically acceptable salts, esters, hydrates, or derivatives, used either  
alone or in combination thereof.
26. A process for preparing a composition according to claim 25, wherein the  
prokinetic agent is domperidone, or its pharmaceutically acceptable salts, esters,  
25 hydrates, or derivatives thereof.
27. A process for preparing a composition according to claim 25, wherein the  
prokinetic agent is metoclopramide, or pharmaceutically acceptable salts, esters,  
hydrates, or derivatives thereof.
28. A process for preparing a composition according to claims 19-27, wherein the  
30 prokinetic agent is co-processed with an organic acid.
29. A process for preparing a composition according to claims 19-28, wherein the  
other pharmaceutically acceptable excipients are selected from the group  
comprising of diluents, binders, disintegrants, colorants, lubricants, plasticizers,

coating agents, opacifiers, antioxidants, and the like used either alone or in combination thereof.

30. A process for preparing a composition according to claim 19, wherein the composition is in the form of tablets filled into hard gelatin capsule.
- 5 31. A process for preparing a composition according to claim 21, wherein the composition is in the form of multilayer tablets.
32. A process for preparing a composition according to claims 19-31, wherein the one prokinetic agent present in the immediate release form and delayed release form is the same.
- 10 33. A process for preparing a composition according to claims 28-32, wherein the ratio of prokinetic agent to the organic acid is 1:0.25 to about 0.25:1.
34. A process for preparing a composition according to claims 28-32, wherein the ratio of prokinetic agent to the organic acid is 1:0.5 to about 0.5:1.
35. A process for preparing a composition according to claims 28-32, wherein the ratio of prokinetic agent to the organic acid is 1:1.
- 15 36. A process for preparing a composition according to claims 19-35, wherein the prokinetic agent is present as 5 to 70 % by weight of total prokinetic agent in immediate release form and the remaining prokinetic agent in delayed release form.
- 20 37. A process for preparing a composition according to claims 19-36, wherein the prokinetic agent present in immediate release form and delayed release form comprises a permeation enhancer.
38. A process for preparing a composition according to claim 37, wherein the permeation enhancer is Vitamin E tocopheryl propylene glycol succinate
- 25 39. A method of treatment of gastro esophageal reflux disease, reflux esophagitis, peptic ulcer, gastric ulcer, and other gastric acid related disorders by administering to a patient in need thereof a pharmaceutical composition as claimed in any of the preceding claims.
40. Use of a composition as claimed in any of the preceding claims for the preparation of a medicament for the treatment of gastro esophageal reflux disease, reflux esophagitis, peptic ulcer, gastric ulcer, and other gastric acid related disorders and the like.
- 30

41. The pharmaceutical composition comprising a gastric acid suppressing agent and one or more prokinetic agent substantially as herein described and illustrated by the examples.
42. The process for the preparation of a pharmaceutical composition comprising a gastric acid suppressing agent and one or more prokinetic agent substantially as  
5 herein described and illustrated by the examples.

Figure 1

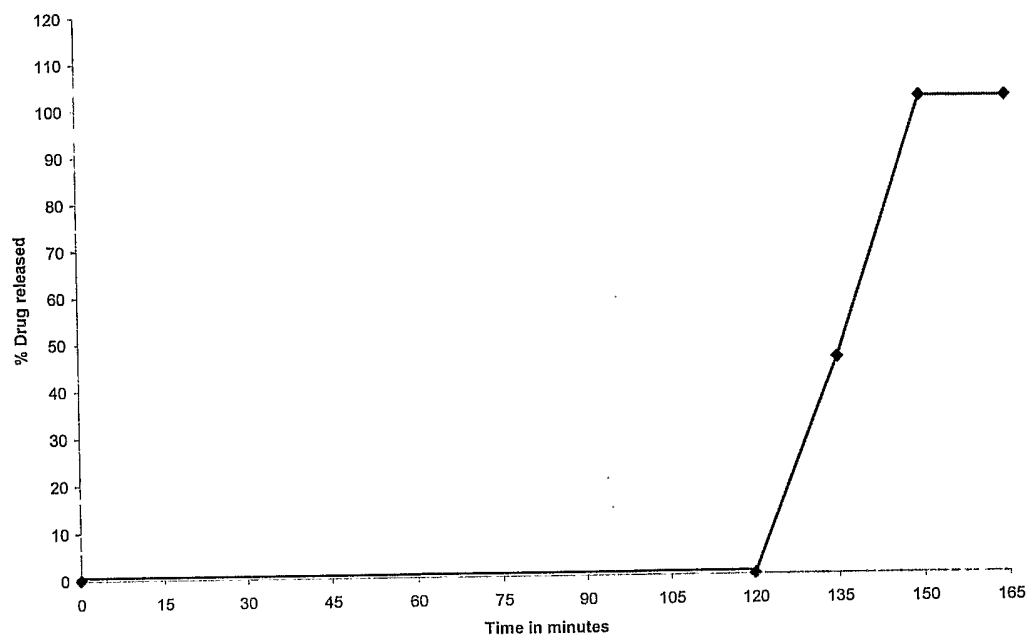
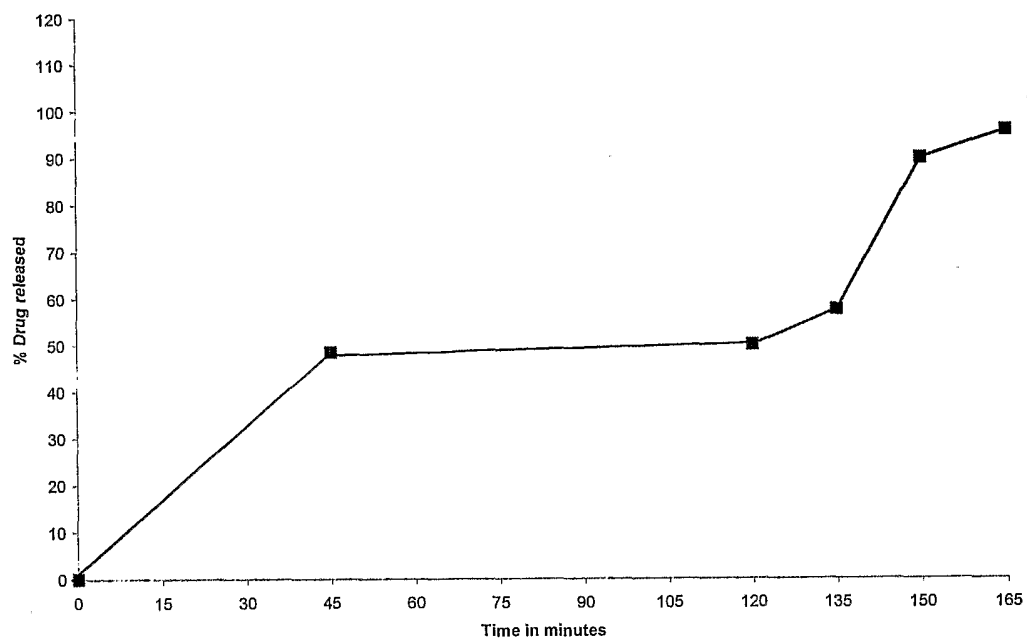


Figure 2



# INTERNATIONAL SEARCH REPORT

national Application No  
PCT/IN2005/000002

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/48 A61K9/50 A61K9/16 A61K9/20 A61K31/136  
A61K31/138 A61K31/4439

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)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                    | Relevant to claim No. |
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| A          | WO 95/01803 A (MERCK & CO., INC;<br>MCNEILL-PPC, INC; SIMS, ROBERT, T; SLIVKA,<br>WILLIAM) 19 January 1995 (1995-01-19)<br>cited in the application<br>page 2, line 32 - page 3, line 31;<br>examples |                       |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 document 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

28 April 2005

Date of mailing of the international search report

06/05/2005

Name and mailing address of the ISA

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Authorized officer

Villa Riva, A

## INTERNATIONAL SEARCH REPORT

national Application No

T/IN2005/000002

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                   | Relevant to claim No. |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN2005/000002

## Box 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.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 39 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 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 additional 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 fee, this Authority did not invite payment of any additional fee.
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.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

RU T/IN2005/000002

| Patent document<br>cited in search report |    | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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