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(57) **Abrégé/Abstract:**

Rapidly dissolving self-supporting films for food or pharmaceutical use comprising: a) a filmogenic substance consisting of a maltodextrin; b) a plasticiser; c) an active principle for food or pharmaceutical use, characterised in that said films are free of hydrocolloids.



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(54) Title: SELF-SUPPORTING FILMS FOR PHARMACEUTICAL AND FOOD USE

(57) Abstract: Rapidly dissolving self-supporting films for food or pharmaceutical use comprising: a) a filmogenic substance con-  
sisting of a maltodextrin; b) a plasticiser; c) an active principle for food or pharmaceutical use, characterised in that said films are  
free of hydrocolloids.

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**SELF-SUPPORTING FILMS FOR PHARMACEUTICAL AND FOOD USE****FIELD OF THE INVENTION**

The present description relates to rapidly dissolving self-supporting films for pharmaceutical or food use

**5 STATE OF THE ART**

Self-supporting films for pharmaceutical or food use have been known for some time.

For example compositions based on edible films are already commercially available. Most of these products use pullulan as the filmogenic component.

10 Pullulan is an expensive ingredient and not easily available. Other materials have been used in place of pullulan. These materials comprise modified starches such as maltodextrin and hydrocolloids such as cellulosic materials, as described for example in US20030053962.

However, these films do not present one or more characteristics typical of pullulan  
15 such as rapid dissolution, clean mouth feel, clean flavour and ease of manufacture.

That these films do not provide a clean mouth sensation is due to the fact that the hydrocolloids tend to gel on contact with saliva.

One solution to the aforesaid drawbacks is proposed in WO03/011259 from which  
20 is noted that, to obtain properties equivalent to those of pullulan, it is crucial that maltodextrin, smaller quantities of hydrocolloid and, additionally, an inert filler are present simultaneously in the filmogenic composition. In this prior patent, therefore, the hydrocolloid content is reduced by virtue of introducing an inert filler at a concentration between 1 and 30% into the film composition. According to  
25 said document, however, the hydrocolloid content cannot be reduced below 10% in that according to this prior patent, as in the preceding US20030053962, the presence of this component in the filmogenic composition appears essential for achieving rapid disintegration of the film.

**TECHNICAL PROBLEM**

30 Therefore the need was felt for a rapidly dissolving edible film which would not pose the problems of known edible films for pharmaceutical or food use.

## SUMMARY OF THE INVENTION

The Applicant has now surprisingly found that self-supporting edible films for food or pharmaceutical use containing maltodextrin as the filmogenic substance can be prepared which dissolve rapidly despite their not containing hydrocolloids.

5 In particular an aspect of the present invention are self-supporting films comprising:

a) a filmogenic substance consisting of a maltodextrin,

b) a plasticiser

c) an active principle for food or pharmaceutical use,

10 characterised in that said films are free of hydrocolloids.

In particular, as seen from the tests described below, the self-supporting films of the invention present disintegration times determined in vitro of less than 1 minute, and in vivo actually less than 45 seconds. Moreover, the self-supporting films impart a clean mouth sensation and in addition can be prepared using  
15 simple preparation methods, easily achievable with industrial machinery.

In this respect a further aspect of the present invention is directed towards various processes for preparing the self-supporting edible films of the present invention.

For example, one preparation process for the aforesaid self-supporting film comprises in particular the following steps:

20 i) the maltodextrin, plasticiser and active ingredient for food or therapeutic use are mixed,

ii) the mixture derived from the preceding step is extruded in an extruder.

Another preparation process according to the present invention comprises in particular the following steps:

25 i) the maltodextrin, plasticiser and active principle for therapeutic or food use are dispersed in a polar solvent,

ii) the mixture obtained in the preceding step is rolled onto silicone paper and then dried,

iii) the silicone paper is removed from the film obtained in the preceding step.

30 Another preparation process according to the present invention comprises in particular the following steps:

i) the maltodextrin, plasticiser and active ingredient for food or therapeutic use are mixed,

ii) the mixture was granulated, sieved and mixed with an anti sticking agent

iii) the granules were stored at least for 12 h

5 iv) the granules derived from the preceding steps were extruded in an extruder for obtaining the edible film.

#### DESCRIPTION OF THE FIGURES

Table 1 in figure 1 shows formulations used for preparing the films of the present invention as described in example 1.

10 Table 2 in figure 2 shows formulations used for preparing the films of the present invention as described in example 2.

Figure 3 shows a graph of the in vivo bioavailability of the film of the present invention prepared as described in example 2 and containing paracetamol (formulation 6 in table 2), and by way of a syrup (Tachipirina syrup), where the y-axis shows paracetamol concentration expressed in  $\mu\text{g/ml}$  whereas the x-axis shows time in minutes.

#### DETAILED DESCRIPTION OF THE INVENTION

The maltodextrin used in the self-supporting film of the present invention has a dextrose content of less than 50 equivalents, preferably between 11 and 40.

20 The plasticiser used in the self-supporting films of the present invention is preferably chosen from the group consisting of polyalcohols, citric acid esters, sebacic acid esters or their mixtures. Propylene glycol, glycerine, sorbitol, maltitol or their relative mixtures are particularly preferred.

The active principle for food use is preferably an active principle with a refreshing action on the breath and indicated for oral hygiene, preferably eugenol and menthol or an active principle suitable for nutritional supplementation, preferably mineral salts chosen from those normally used for such purposes or one or more vitamins, the vitamin being ascorbic acid in a particularly preferred embodiment.

25 The active principle for therapeutic use can be a principle with an essentially topical activity for the oral cavity chosen from antibacterial, antimycotic, antiviral agents or disinfectants of the oral cavity, or can be an active principle with an

essentially systemic action chosen from the class consisting of anti-inflammatory, analgesic, antipsychotic, hypnotic, anxiolytic, antihypertensive, myorelaxant, antimigraine, antiparkinsonian, antiemetic, antihistaminic, beta blocking and antiasthmatic agents.

- 5 The active principles contained in said films are preferably chosen from the class consisting of: Piroxicam, Ketoprofen, Sodium diclofenac, Tramadol hydrochloride, Morphine, Nifedipine, Diazepam, Lorazepam, Alprazolam, Bromazepam, Triazolam, Lormetazepam, Zolpidem, Paracetamol, Selegiline, Atenolol, Salbutamol, Sumatriptan, Clozapine, Cetirizine, Ondansetron, Fentanyl and their  
10 pharmaceutically acceptable salts.

The self-supporting films of the present invention contain maltodextrin in concentrations preferably between 40 and 80% by weight, plasticiser in concentrations between 15 and 55% by weight and active principle for food or pharmaceutical use in quantities between 0.05 and 30% by weight on the total  
15 weight of said film, and can possibly contain other excipients chosen from antisticking agents such as microcrystalline cellulose, colloidal silica or talc, sweeteners, flavourings, colouring agents, preservatives, acidity regulating systems or mixtures thereof.

In the process for preparing edible self-supporting films by extrusion, a further  
20 aspect of the present invention, the extrusion step (ii) is preferably conducted at a temperature between 60 and 120°C in a single screw extruder. In the second preparation process, a further aspect of the present invention, the polar solvent used in step (i) is preferably chosen from water, water-miscible solvents or relative mixtures. In accordance with a particularly preferred embodiment the  
25 solvent consists of water or a mixture of water and ethanol. The temperature of said step, when a mixture of the aforesaid solvents are used, is preferably between 60 and 105°C.

The self-supporting films of the present invention can be prepared using other methods such as by compacting the filmogenic formulation by the ultrasound  
30 technique.

Some examples of formulations for the self-supporting films of the present

invention, some processes for preparing said self-supporting films, as well as in vitro and in vivo disintegration tests conducted on films obtained with some of the illustrated formulations are given by way of non limiting examples.

### **EXAMPLE 1 – Films prepared by extrusion**

#### *Preparation method*

The components of the formulations given in table 1 of figure 1 are mixed and extruded with a single screw extruder at a temperature of 105°C.

#### *Disintegration assay*

The test was undertaken in accordance with the method in the European Pharmacopoeia 5.01 Ed., 2.9.1. Disintegration of tablets and capsules (01/2005:20901)

Purified water maintained at 37°C was used as the medium. The result is the average of 3 determinations  $\pm$  standard deviation.

The results are given in table 3.

Table 3: Disintegration time

| Form. no. | Disintegration time (in seconds) |
|-----------|----------------------------------|
| 2         | 50 $\pm$ 4                       |
| 5         | 54 $\pm$ 4                       |
| 6         | 40 $\pm$ 1                       |
| 8         | 30 $\pm$ 1                       |
| 11        | 32 $\pm$ 2                       |
| 17        | 19 $\pm$ 1                       |

#### *In vivo dissolution assay*

Three 4 cm<sup>2</sup> samples of the formulation under examination were administered to 6 healthy volunteers. The test consists of retaining the film sample in the mouth, and determining the time needed to sense its disappearance.

The test was conducted on formulations no. 2, 5, 17 (table 1).

In each case dissolution time was less than a minute.

**EXAMPLE 2 – Films prepared by spreading and evaporation of the solvent.***Preparation method*

The components of the formulations given in table 2 of figure 2 are dispersed in the mixture of solvents, given in the same table, and maintained at 80°C. The mixture, maintained at the same temperature, is rolled onto silicon paper and dried.

*Disintegration assay*

The test was undertaken in accordance with the method in the European Pharmacopoeia 5.01 Ed., 2.9.1. Disintegration of tablets and capsules (01/2005:20901)

Purified water maintained at 37°C was used as the medium. The result is the average of 3 determinations  $\pm$  standard deviation.

The results are given in table 4

Table 4: Disintegration time

| Form. no. | Disintegration time (in seconds) |
|-----------|----------------------------------|
| 4         | 27 $\pm$ 4                       |
| 5         | 36 $\pm$ 4                       |
| 6         | 50 $\pm$ 3                       |
| 7         | 37 $\pm$ 8                       |
| 13        | 32 $\pm$ 2                       |

*In vivo dissolution assay*

A 4 cm<sup>2</sup> sample of the formulation under examination was administered to each of 6 healthy volunteers. The test consists of retaining the film sample in the mouth, and determining the time needed to sense its disappearance.

The test was conducted on formulations no. 3, 6, 13 (table 1).

In each case dissolution time was less than 45 seconds.

*Determination of in vivo bioavailability*

The object of this pilot study was to evaluate the absorption and pharmacokinetic profile after a single administration of 50 mg paracetamol carried by Formula 6 (table 2) and by a commercial syrup containing paracetamol (Tachipirina syrup) in 3 healthy volunteers aged between 23 and 24 years. The experiment was conducted as a crossover with a 15 day wash-out period.

With the aim of evaluating the pharmacokinetic profiles of the two formulations, saliva and blood samples were taken before application and at 10 min, 20 min, 45 min, 1 h, 2 h, 3 h, 4 h, 6 h after administration. Paracetamol was determined in the saliva.

The salivary concentrations of paracetamol determined in saliva after administration of the syrup and of the rapidly disintegrating film overlap completely as shown in figure 3.

### EXAMPLE 3 – Films prepared by granulation and extrusion

#### Film composition

| <u>Components</u>          | <u>Formulation</u><br><u>A</u><br><u>(%m/m)</u> | <u>Formulation</u><br><u>B</u><br><u>(%m/m)</u> | <u>Formulation</u><br><u>C</u><br><u>(%m/m)</u> | <u>Formulation</u><br><u>D</u><br><u>(%m/m)</u> |
|----------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Maltodextrin (DE 11)       | 71                                              | 47                                              | 70                                              | 71.4                                            |
| Glycerol                   | 16                                              | -                                               | 16                                              | 16.5                                            |
| Menthol                    | 1                                               | -                                               | -                                               | -                                               |
| Microcrystalline cellulose | 12                                              | 10                                              | 12                                              | 12                                              |
| Paracetamol                | -                                               | 21                                              | -                                               | -                                               |
| Ondansetron                | -                                               | -                                               | 2                                               | -                                               |
| Fentanyl                   | -                                               | -                                               | -                                               | 0.1                                             |
| Propylene Glycol           | -                                               | 20                                              | -                                               | -                                               |
| Sodium citrate             | -                                               | 2                                               | -                                               | -                                               |

#### ***Preparation method***

The components, with the exception of the microcrystalline cellulose, were mixed into a sigma blade mixer; the time of mixing was 1 hour for formulation B and 30

minutes for formulation A, C and D.

The mixture was transferred in an oscillating granulator and microcrystalline cellulose was added as antisticking agent. The granules are stored for at least 12 hours at ambient temperature and then sieved.

5 The granules were extruded with a single screw extruder. The extruder temperatures were set in the range 85-130°C .

#### *Disintegration test*

10 The test was undertaken in accordance with the method in the European Pharmacopoeia 5.01 Ed., 2.9.1. Disintegration of tablets and capsules (01/2005:20901)

Purified water maintained at 37°C was used as the medium. The results were the average of 3 determinations  $\pm$  standard deviation.

The disintegration times were less of 45 sec for all the formulations.

15

#### *In vivo dissolution assay*

Three 4 cm<sup>2</sup> samples of the formulation A were administered to 6 healthy volunteers. The test consists of retaining the film sample in the mouth, and determining the time needed to sense its disappearance.

20 In each case dissolution time was less than 15 sec.

## CLAIMS

1. A self-supporting edible film comprising:
  - a) a filmogenic substance consisting of a maltodextrin,
  - 5 b) a plasticiser wherein the plasticiser is a polyalcohol, a citric acid ester or a sebacic acid ester or a mixture thereof,
  - c) an active ingredient for food or pharmaceutical use,wherein said film is free of hydrocolloids.
- 10 2. The self-supporting film as claimed in claim 1, wherein the maltodextrin (a) has a dextrose content of less than 50 expressed in equivalents.
3. The self-supporting film as claimed in claim 2 wherein said dextrose content is between 11 and 40.
- 15 4. The self-supporting film as claimed in any one of claims 1-3, wherein the plasticiser is propylene glycol, glycerine, sorbitol or maltitol, or a mixture thereof.
5. The self-supporting film as claimed in any one of claims 1-4, wherein the  
20 active principle for food use is an active principle with a breath freshening action and/or indicated for oral hygiene or an active principle suitable for nutritional supplementation.
6. The self-supporting film as claimed in claim 5, wherein said active principle  
25 for food use is menthol or eugenol.
7. The self-supporting film as claimed in claim 5, wherein said active principle suitable for nutritional supplementation is a mineral salt or a vitamin.
- 30 8. The self-supporting film as claimed in claim 7, wherein the vitamin is ascorbic acid.

9. The self-supporting film as claimed in any one of claims 1-4, wherein said active principle for pharmaceutical use is a topically active principle.

10. The self-supporting film as claimed in claim 9, wherein said active principle is  
5 an antibacterial, an antimycotic, an antiviral agent or a disinfectant of the oral cavity.

11. The self-supporting film as claimed in any one of claims 1-4, wherein the active principle for pharmaceutical use is a systemically active principle.

10

12. The self-supporting film as claimed in claim 11, wherein said active principle is an anti-inflammatory, an analgesic, an antipsychotic, a hypnotic, an anxiolytic, an antihypertensive, a myorelaxant, an antimigraine, an antiparkinsonian, an antiemetic, an antihistaminic, a beta blocking or an antiasthmatic agent.

15

13. The self-supporting film as claimed in claim 11 or 12, wherein said principle is Piroxicam, Ketoprofen, Sodium diclofenac, Tramadol hydrochloride, Morphine, Nifedipine, Diazepam, Lorazepam, Alprazolam, Bromazepam, Triazolam, Lormetazepam, Zolpidem, Paracetamol, Selegiline, Atenolol,  
20 Salbutamol, Sumatriptan, Clozapine, Cetirizine, Ondansetron, or Fentanyl, or a pharmaceutically acceptable salt thereof.

14. The self-supporting film as claimed in any one of claims 1-13, wherein maltodextrin is in a concentration between 40 and 80% by weight, plasticiser is  
25 in a concentration between 15 and 55% by weight and the active principle for food or pharmaceutical use is in a concentration between 0.05% and 30% by weight, on the total weight of said film.

15. The self-supporting film as claimed in any one of claims 1-14, further  
30 containing an excipient, wherein the excipient is an antisticking agent, a sweetener, a flavouring, a colouring agent, a preservative, or an acidity regulating system, or a mixture thereof.

16. The self-supporting film as claimed in claim 15, wherein said antisticking agent is microcrystalline cellulose, colloidal silica or talc.

5 17. A process for preparing the self-supporting film claimed in any one of claims 1-16, comprising the following steps:

- i) the maltodextrin, plasticiser and active principle for food or pharmaceutical use are mixed,
- ii) the mixture derived from the preceding step is extruded in an extruder.

10

18. The process as claimed in claim 17, wherein the extrusion step (ii) is conducted at a temperature between 60 and 120°C.

15

19. The process as claimed in claim 17 or 18 the process being conducted in a single screw extruder.

20. A process for preparing the self-supporting film claimed in any one of claims 1-16, comprising the following steps:

- i) the maltodextrin, plasticiser and the active principle for pharmaceutical or food use are dispersed in a polar solvent at a temperature between 60 and 105°C,
- 20 ii) the mixture obtained in the preceding step is rolled onto silicone paper and then dried,
- iii) the silicone paper is removed from the film obtained in the preceding step.

25 21. The process as claimed in claim 20, wherein the polar solvent used in step (i) is water, or a water miscible solvent, or a mixture thereof.

22. The process as claimed in claim 21, wherein said solvent consists of water or a water-ethanol mixture.

30

23. The process as claimed in claim 22, wherein the temperature of steps (i) and (ii) is between 60 and 105°C.

24. A process for preparing the self-supporting film claimed in any one of claims 1-16, comprising the following steps:

- 5 i) the maltodextrin, plasticiser and active ingredient for food or pharmaceutical use are mixed,
- ii) the mixture was granulated, sieved and mixed with an anti sticking agent,
- iii) the granules were stored at least for 12 h,
- iv) the granules derived from the preceding step were extruded in an extruder for obtaining the edible film.

10

25. The process as claimed in claim 24, wherein the extrusion step (ii) is conducted at a temperature between 70 and 140°C.

26. The process as claimed in claims 17 or 18 or 25 the process being  
15 conducted in a single screw extruder.

1/3

Figure 1

Table 1 – Formulations used for preparing films by extrusion

| Form. no. | MD DE 40 (g) | MD DE1 1 (g) | GP (g) | SB (g) | SC (g) | PRX (g) | KP (g) | DS (g) | TR (g) | NF (g) | ZPD (g) | LRZ (g) | BRZ (g) | TRZ (g) | MR (g) | MTC (g) | MEN (g) | A-AC (g) | SLG (g) | ATL (g) | SAL (g) | SMT (g) | CZP (g) | SLG (g) | CTZ (g) | SBT (g) |
|-----------|--------------|--------------|--------|--------|--------|---------|--------|--------|--------|--------|---------|---------|---------|---------|--------|---------|---------|----------|---------|---------|---------|---------|---------|---------|---------|---------|
| 1         | 40           |              | 10     |        |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 2         | 40           |              | 7      | 3      |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 3         | 45           |              | 3.5    | 1.5    |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 4         | 40           |              | 3      | 7      |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 5         | 80           |              | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 6         | 72           |              | 9      | 9      |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 7         |              | 80           | 10     | 10     |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 8         |              | 72           | 9      | 9      |        |         | 10     | 12     |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 9         |              | 70           | 9      | 9      |        |         |        |        | 20     |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 10        |              | 62           | 9      | 9      |        |         |        |        |        | 10     |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 11        | 80           |              | 10     | 10     |        |         |        |        |        |        | 10      |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 12        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 13        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         | 0.5     |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 14        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         |         | 0.3     | 10      |        |         |         |          |         |         |         |         |         |         |         |         |
| 15        | 80           |              | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         | 20     |         |         |          |         |         |         |         |         |         |         |         |
| 16        |              | 62           | 9      | 9      |        |         |        |        |        |        |         |         |         |         |        | 10      |         |          |         |         |         |         |         |         |         |         |
| 17        | 80           |              | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 18        |              | 40           | 3      | 7      |        |         |        |        |        |        |         |         |         |         |        |         | 0.1     | 5        |         |         |         |         |         |         |         |         |
| 15        | 75           |              | 9      | 9      | 0.2    |         |        |        |        |        |         |         |         |         |        |         |         |          |         | 20      |         |         |         |         |         |         |
| 16        |              | 62           | 9      | 9      |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 17        | 58           |              | 8      | 8      |        |         |        |        |        |        |         |         |         |         |        |         |         |          |         | 25      |         |         |         |         |         |         |
| 18        |              | 9            | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 19        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 20        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         | 10      |         |         |
| 21        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         |         |         |
| 22        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         | 10      |         |         |
| 23        |              | 80           | 10     | 10     | 0.4    |         |        |        |        |        |         |         |         |         |        |         |         |          |         |         |         |         |         |         | 10      |         |

\*MTD: maltodextrin; DE: Dextrose equivalents; GP: propylene glycol; SB: sorbitol; SC: colloidal silica; PRX: piroxicam; KP: ketoprofen DS: Sodium diclofenac; TR: Tramadol hydrochloride; MR: Morphine sulfate; NF: Nifedipine; LRZ: Lorazepam; TRZ: Triazolam; BRZ: Bromazepam; ZPD: Zolpidem; MTC: Methoclopramide; MEN: Menthol; A-As: Ascorbic Acid; SLG: Selegiline; ATL: Atenolol; SAL: Salbutamol; SMT: Sumatriptan; CZP: Clozapine; CTZ: Ceftriaxone

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Figure 2

Table 2 - Formulations used for preparing the films

| Form.<br>n. | MD<br>DE<br>40<br>(%) | MD<br>DE 11<br>(%) | GP<br>(%) | SB<br>(%) | MT<br>(%) | TC<br>(%) | Water<br>(%) | Ethanol<br>(%) | SC<br>(%) | GLI<br>(%) | PRX<br>(%) | PRC<br>(%) | DS<br>(%) | NF<br>(%) | CLO<br>(%) | EU<br>(%) | CPT<br>(%) | TIO<br>(%) | DMS<br>(%) | ATEC<br>(%) | DB<br>S<br>(%) |
|-------------|-----------------------|--------------------|-----------|-----------|-----------|-----------|--------------|----------------|-----------|------------|------------|------------|-----------|-----------|------------|-----------|------------|------------|------------|-------------|----------------|
| 1           | 25                    |                    | 15        |           |           |           | 10           |                |           |            |            |            |           |           |            |           |            |            |            |             |                |
| 2           | 70                    |                    | 13        |           | 2         |           | 6            |                |           |            |            |            |           |           |            |           |            |            |            |             |                |
| 3           | 31.2                  |                    | 5.8       |           | 18        |           | 13.5         |                |           |            |            |            |           |           |            |           |            |            |            |             |                |
| 4           | 70                    |                    |           | 5         | 2.5       |           | 50           | 14             |           | 14         |            |            |           |           |            |           |            |            |            |             |                |
| 5           | 46.5                  |                    | 10        | 7.4       | 0.4       |           | 26           | 7.9            | 0.1       |            | 14         | 4.8        |           |           |            |           |            |            |            |             |                |
| 6           | 46.5                  |                    | 15        | 5         | 0.6       |           | 26           | 12             | 0.2       |            |            | 18         |           |           |            |           |            |            |            |             |                |
| 7           | 34.4                  |                    | 11.2      | 3.7       | 0.5       | 8.4       | 19.4         | 9.7            | 0.2       |            |            | 13.4       |           |           |            |           |            |            |            |             |                |
| 8           | 46.5                  |                    | 15        | 5         | 0.6       |           | 26           | 20             | 0.2       |            |            |            | 18        |           |            |           |            |            |            |             |                |
| 9           | 46.5                  |                    | 15        | 5         | 0.6       |           | 26           | 12             | 0.2       |            |            |            |           | 3.6       |            |           |            |            |            |             |                |
| 10          | 46.5                  |                    | 15        | 5         | 0.6       |           | 26           | 12             | 0.2       |            |            |            |           |           | 0.8        |           |            |            |            |             |                |
| 11          | 50                    |                    | 30        |           |           |           | 20           |                |           | 10         |            |            |           |           |            |           |            |            |            |             |                |
| 12          | 50                    |                    | 20        |           |           |           | 20           |                | 0.2       | 5          |            |            |           |           |            |           |            |            |            |             |                |
| 13          | 50                    |                    | 20        |           |           |           | 20           |                | 0.2       |            |            |            |           |           |            | 0.1       | 18         |            |            |             |                |
| 14          | 46.5                  |                    | 15        | 5         | 0.6       |           | 26           | 12             | 0.2       |            |            |            |           |           |            |           |            | 18         |            |             |                |
| 15          | 46.5                  |                    | 15        | 5         | 0.6       |           | 26           | 12             | 0.2       |            |            |            |           |           |            |           |            |            | 0.5        |             |                |
| 16          | 46.5                  |                    | 10        | 7.4       | 0.4       |           | 26           | 7.9            | 0.1       |            |            | 4.8        |           |           |            |           |            |            |            |             |                |
| 17          | 46.5                  |                    | 15        | 5         | 0.6       |           | 26           | 12             | 0.2       |            |            |            |           |           |            |           |            |            |            | 10          |                |
| 18          | 46.5                  |                    |           | 5         | 0.6       |           | 26           | 12             | 0.2       |            |            |            |           |           |            |           |            |            |            |             | 8              |
| 19          | 46.5                  |                    |           | 7.4       | 0.4       |           | 26           | 7.9            | 0.1       |            |            | 4.8        |           |           |            |           |            |            |            |             |                |

\*MTD: maltodextrin; DE: Dextrose equivalents; GP: propylene glycol; SB: sorbitol; MT: maltitol; TC: Talc PRX: piroxicam; KP: ketoprofen DS: Sodium diclofenac; MR: Morphine sulfate; NF: Nifedipine; CLO: Clonazepam; BRZ: Bromazepam; ZPD: Zolpidem; PRC: Paracetamol; EU: Eucalyptus; SC: sodium citrate; CPT: captopril; TIO: thiocolchicoside; DMS:dexamethasone; ATEC: Acetyltrethyl citrate;DBS: dibutyl sebacate.

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Figure 3

