TITLE OF THE INVENTION

RAPID ONSET FORMULATION

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a rapid onset formulation, preferably in form of an enterically coated tablet, for a medicament comprising a synergistic duo of active ingredients namely, doxylamine succinate and pyridoxine HCl, hereinafter referred to as "DS-P". DS-P is useful in the treatment of nausea and vomiting, especially, but not limited to, during pregnancy, hereinafter referred to as "NVP". Thus the present invention is concerned with all known and future therapeutic indications of DS-P.

THE PRIOR ART

Pharmaceutical formulations of DS-P are known. The current formulation, commercially available in Canada under the name Diclectin (Duchesnay Inc.) comprises the following active ingredients: pyridoxine HCl and Doxylamine succinate. It additionally comprises the following excipients: lactose, microcrystalline cellulose, magnesium trisilicate, silicon dioxide and magnesium stearate.

Diclectin is the world's most studied drug in regard to its safety during pregnancy. Because of its excellent safety profile, Diclectin is the drug of choice for the treatment of NVP. The current formulation is sugar coated and suffers from drawbacks, one of which being its delayed onset of action. However, the current formulation once ingested, can take more than 4 hours before the two active ingredients (pyridoxine HCl and doxylamine succinate) reach nearly full dissolution in the small intestines, where it is

absorbed. This delay is often considered too long for patients, such as women suffering from NVP, who require urgent relief of symptoms.

Another drawback of the current formulation is related to patient compliance. Women suffering from NVP often complain of hyper olfaction, which means that various odors and tastes can trigger nausea or vomiting problems. The smell and taste of sugar on the current sugar coated formulation as well as the use of organic solvents and phthalates in the preparation of the currently used enteric coating, bothers many pregnant women to the point where the intake of the drug is essentially inhibited.

The size of the currently available tablet is also problematic. A smaller size tablet would improve patient compliance since women suffering from NVP often have problems swallowing. Furthermore, a smaller tablet looks less harmful than a bigger one and patients will have the impression that they are taking a lesser amount of drug. This will in turn significantly increase patient compliance.

Finally, the current formulation contains lactose. This is objectionable for those patients suffering from lactose intolerance.

Thus, it is desirable to provide patients suffering from nausea and vomiting an improved rapid onset formulation overcoming the drawbacks of the prior art.

However, since DS-P is orally delivered as an enteric coated tablet, the novel oral formulation must transit through the stomach unscathed and rapidly release both active ingredients once the dosage form reaches its intended destination, namely the intestines.

The main challenge surmounted by the present invention was to arrive at a dosage form capable of overcoming the drawbacks of the prior art while simultaneously delivering the synergistic duo of active ingredients for rapid onset. It was also important to provide a formulation exhibiting similar dissolution curves for both active ingredients so as to avoid the dissolution of one active ingredient to the detriment of the other. This was important in view of the synergistic therapeutic effect of the duo of active ingredients.

SUMMARY OF THE INVENTION

A first aspect of the present invention provides an enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation comprising a disintegrating agent such that the following dissolution profiles are satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

(a) at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 30 minutes of measurement;

(b) at least about 70% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 60 minutes of measurements.

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 90 minutes of measurement;

(d) at least about 90% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 120 minutes of measurement.

A second aspect of the present invention provides a use of the rapid onset formulation as defined in the first aspect in the preparation of a

medicament for treating nausea and vomiting in a patient in need thereof.

A third aspect of the present invention provides a use of the rapid onset formulation as defined in the first aspect in the preparation of a medicament for treating nausea and vomiting during pregnancy in a patient in need thereof.

A fourth aspect of the present invention provides a medicament for attenuating the symptoms associated with nausea and vomiting consisting essentially of the formulation as defined above.

A fifth aspect of the present invention provides a process of preparing the rapid onset formulation as defined above, said process comprising the steps of:

- blending said doxylamine succinate and said silica flow conditioner to obtain a pre-blend;
- mixing said preblend with said pyridoxine HCl to obtain an active ingredient blend;
- mixing said active ingredient blend with said remaining non-active excipients, namely: a filler or binder, a disintegrating agent, a lubricant, and a stailizing agent to obtain a final blend; and
- tabletting and coating said final blend.

Disclosed herein is a new aqueous enteric-coated formulation comprising DS-P, the formulation exhibiting a dissolution profile indicative of a rapid onset.

Further disclosed herein is a pharmaceutical composition having *specific in-vitro* dissolution profiles indicative of rapid onset of the active ingredients. The pharmaceutical composition being suitable for simple and reproducible manufacture.

Further scope of applicability will become apparent from the detailed description given hereinafter. It should be understood however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

DESCRIPTION OF THE DRAWINGS

Figure 1 depicts two examples of dissolution profiles in accordance to the rapid onset formulation of the present invention in comparison to a

dissolution profile of the prior art formulation. The first dissolution profile (example 1) corresponds to a rapid onset formulation from which nearly 100% of both active ingredients is released within 45 minutes. The second dissolution profile (example 2) corresponds to a rapid onset formulation from which approximately 95% of both active ingredients is released within 120 minutes. The last and comparative dissolution profile (prior art) corresponds to the currently available formulation from which approximately 100% of the pyridoxine HCl and approximately 90% of the doxylamine succinate is released within 240 minutes.

Figure 2 is a schematic flowchart of the preferred manufacturing process of a preferred formulation in accordance with the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Other objects and attendant features of the present invention will become readily appreciated, as the same becomes better understood by reference to the following detailed description of a preferred embodiment described for the purpose of illustration.

In a broad sense, the invention provides a rapid onset formulation comprising pyridoxine HCl and doxylamine succinate.

The formulation of the present invention may be used in the human and veterinary fields of medicine whenever symptoms of nausea and/or vomiting require medical intervention. Since the formulation of the present invention is intended for medicinal purposes, then the formulation and its components should be pharmaceutically acceptable. The preferred formulation is in the form of an oral dosage form such as a tablet, pill or encapsulated beads or solution. The most preferred formulation is a tablet.

The tablet of the present invention is preferably capable of transiting through the stomach unscathed. To test this feature, the tablet of the present invention was tested to resist disintegration in simulated gastric fluid "SGF" for a minimum period of 1 hour.

In accordance with the present invention, the formulation will satisfy the following dissolution profiles when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm; preferably measured by high performance liquid chromatography:

(a) at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 30 minutes of measurement;

(b) at least about 70% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 60 minutes of measurement;

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 90 minutes of measurement;

(d) at least about 90% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 120 minutes of measurement;

In the present invention, any reference to dissolution profile should be construed as referring to the results of a dissolution test in which the amount of pyridoxine HCl and of doxylamine succinate released is measured in 1000 ml phosphate buffer at pH 6.8 and 37°C using a USP (United States Pharmacopoeia) type 2 dissolution apparatus at 100 rpm; preferably measured by high performance liquid chromatography.

As used herein and in the claims, an "enteric coating" is understood to mean a coating comprising one or more layers generally resistant to disintegration in human gastric fluids, but which will disintegrate in human intestinal fluids, as well as coatings which disintegrate very slowly in human gastric fluids, but more rapidly in human intestinal fluids. In a broad sense, "enteric coating" can encompass for example any seal coat placed on the compressed core of a tablet prior to the enteric coating *per se* as well as any finishing aesthetic coat placed on the enteric coating *per se*.

In a most preferred embodiment, the formulation of the present invention contains a core coated with an aqueous enteric coating. The core comprises the active ingredients pyridoxine HCl and doxylamine succinate along with non-active excipients such as a filler or binder, a disintegrating agent, a lubricant, a silica flow conditioner and a stabilizing agent.

Examples of fillers or binders include acacia, alginic acid, calcium phosphate (dibasic), carboxymethylcellulose, carboxymethylcellulose sodium, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, dextrin, dextrates, sucrose, tylose, pregelatinized starch, calcium sulfate, amylose, glycine, bentonite, maltose, sorbitol, ethylcellulose, disodium hydrogen phosphate, disodium phosphate, disodium pyrosulfite, polyvinyl alcohol, gelatin, glucose, guar gum, liquid glucose, compressible sugar, magnesium aluminum silicate, maltodextrin, polyethylene oxide, polymethacrylates, povidone, sodium alginate, tragacanth microcrystalline cellulose, starch, and zein. A most preferred filler or binder consists of microcrystalline cellulose.

Examples of disintegrating agents include alginic acid, carboxymethylcellulose, carboxymethylcellulose sodium,

hydroxypropylcellulose (low substituted), microcrystalline cellulose, powdered cellulose, colloidal silicon dioxide, sodium croscarmellose, crospovidone, methylcellulose, polacrilin potassium, povidone, sodium alginate, sodium starch glycolate, starch, disodium disulfite, disodium edathamil, disodium edetate, disodiumethylenediaminetetraacetate (EDTA) crosslinked polyvinylpyrollidines, pregelatinized starch, carboxymethyl starch, sodium carboxymethyl starch, microcrystalline cellulose. A most preferred disintegrating agent consists of sodium crosscarmelose.

Examples of lubricants include calcium stearate, canola oil, glyceryl palmitostearate, hydrogenated vegetable oil (type I), magnesium oxide, magnesium stearate, mineral oil, poloxamer, polyethylene glycol, sodium lauryl sulfate, sodium stearate fumarate, stearic acid, talc and, zinc stearate, glyceryl behapate, magnesium lauryl sulfate, boric acid, sodium benzoate, sodium acetate, sodium benzoate/sodium acetate (in combination), DL leucine. A most preferred lubricant consists of magnesium stearate.

Examples of silica flow conditioners include colloidal silicon dioxide, magnesium aluminum silicate and guar gum. A most preferred silica flow conditioner consists of silicon dioxide.

Examples of stabilizing agents include acacia, albumin, polyvinyl alcohol, alginic acid, bentonite, dicalcium phosphate, carboxymethylcellulose, hydroxypropylcellulose, colloidal silicon dioxide, cyclodextrins, glyceryl monostearate, hydroxypropyl methylcellulose, magnesium trisilicate, magnesium aluminum silicate, propylene glycol, propylene glycol alginate, sodium alginate, carnauba wax, xanthan gum, starch, stearate(s), stearic

acid, stearic monoglyceride and stearyl alcohol. A most preferred stabilizing agent consists of magnesium trisilicate.

In a preferred embodiment, the core of the new rapid onset Diclectin formulation will contain approximately about 4 to 10%, most preferably about 7% by weight of pyridoxine HCl; about 4 to10%, most preferably about 7% by weight of doxylamine succinate; about 40 to 80%, most preferably about 62% by weight of microcrystalline cellulose; about 10 to 30%, most preferably about 18% by weight of magnesium trisilicate; about 0.5 to 5%, most preferably about 1% by weight of silicon dioxide; 0.5 to 5% most preferably about 3% by weight of sodium croscarmellose and about 0.5 to 5%, most preferably about 3% by weight of magnesium stearate.

Example 1

The following is an example of a 145 mg Diclectin rapid onset core formulation:

Table 1: Core Ingredients:

Ingredients	Weight Mg/Tab.	Weight % / Tab.	Batch size 100 kg
Doxylamine Succinate	10.0	6.9	6.897
Pyridoxine HCl	10.0	6.9	6.897
Magnesium trisilicate	26.4	18.2	18.207
Microcrystalline Cellulose PH 102	90.0	62.1	62.069
Sodium Croscarmellose Type A	3.6	2.5	2.483
Magnesium Stearate	4.0	2.8	2.759
Silicon Dioxide NF	1.0	0.7	0.690
Total:	145.0	100	100

The core can then be enterically coated with an aqueous enteric coating which will allow the formulation to transit through the stomach relatively unscathed while allowing rapid dissolution in the intestines.

The coating formulation can be as follows:

Table 2: Coating Formulation

Ingredients	Weight Mg/Tab.	Weight %	Batch size 100kg
Seal Coat			
Opadry™ Clear YS-1-7472	4.82	3.33	3.327
Purified Water USP			
Total:	4.82	3.33	3.33
Enteric Coat			
Estacryl™ 30D Enteric Coating Solution*	39.58	27.29	27.294
Talc USP 200 Mesh	2.85	1.97	1.968
Polyethylene Glycol 400 USP	1.20	0.83	0.826
Antifoam 1520	0.12	0.08	0.081
Purified Water USP			
Total:	16.04	30.17	30.17
Finishing Coat			
Opadry™ White YS-1-7003	1.61	1.11	1.108
Purified Water USP			
Total:	1.61	1.11	1.11

*Estacryl 30D Enteric Coating Solution contains 30% of solids. Therefore, the total actual enteric coating amounts to 11.07%.

Total coated tablet weight 167.47 mg.

The purpose of the seal coat is to provide a smooth surface for the enteric coating, thereby avoiding mounds, pits or crevasses wherein uneven amounts of enteric coating would be applied.

Dissolution Data

The rapid onset formulation of the previous example has exhibited in-vitro dissolution profiles as shown in Table 3 below, when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm. The numerical values are expressed as percentages of dissolved active ingredient in relation to starting quantities.

Table 3: Dissolution profiles

Pyridoxine HCl	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Avg.
5 minutes	20	2	0	77	79	79	43
10 minutes	91	90	90	91	94	95	92
15 minutes	96	96	94	94	95	96	95
30 minutes	95	98	96	95	98	96	96
45 minutes	97	96	97	94	99	98	97
Doxylamine Succinate	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Avg.
5 minutes	17	2	0	70	75	76	40
10 minutes	90	87	89	89	97	96	91
15 minutes	98	97	96	92	98	97	96
30 minutes	97	98	96	94	99	97	97
45 minutes	98	96	98	92	100	99	97

The extremely low dissolution values obtained after 5 minutes for runs 1 to 3, can be explained by the non-disintegration of the core formulation at the 5 minute interval.

Example of method of manufacture

The formulation of the present invention was prepared using the ingredients shown in Table 1, above. Doxylamine succinate and silicon dioxide NF are pre-blended in a 2 cu. Ft. V-Blender. The resulting pre-blend is then milled through a Quadro Co Mill, Model 196S, equipped with a 40 mesh screen.

Pyridoxine HCl is also milled through a Quadro Co Mill, Model 196S, equipped with a 40 mesh screen. The milled pyridoxine HCl is then combined with the doxylamine / silicon dioxide NF pre-blend and the combined mixture blended.

Microcrystalline Cellulose is milled through a 40 mesh screen and split into two approximately equal portions. One portion is subsequently combined in a 650L Gallay Bin with the previously formed pre-blend containing both the active ingredients, followed by the addition of the second portion. The loaded material is then blended followed by the addition of magnesium trisilicate and sodium croscarmellose. The newly formed mixture is blended. The addition of magnesium stearate followed by an additional blending completes the preparation of the core formulation.

The final blend is compressed in tablet form and is subsequently seal coated, enteric coated using a suitable commercially available aqueous enteric coating and top coated for aesthetics. The overall manufacturing process is depicted in Figure 2.

All coating steps using the ingredients of Table 2, namely, the seal coat on the core, the enteric coating and the opadry white (color coat) are

advantageously performed in a Vector Hi (trade-mark) coater pan equipped with a peristaltic pump.

Example 2

The following is another example of a 146 mg Diclectin rapid onset core formulation. The formulation was manufactured along the same manufacturing methods as described above in example 1. This example demonstrates that the rapid onset feature of the formulation of the present invention was obtained with a different group of excipients.

Table 4: Core Ingredients:

Ingredients	Weight Mg/Tab.	Weight %/Tab.
Doxylamine Succinate	10.5	7.2
Pyridoxine HCl	10.5	7.2
Magnesium trisilicate	30.0	20.6
Microcrystalline Cellulose PH 102	65.0	44.5
Calcium Phosphate (Dibasic)	25.0	17.1
Magnesium Stearate	4.0	2.7
Colloidal Silicon Dioxide	1.0	0.7
Total:	146.0	100

The coating formulation can be as follows:

Table 5: Coating Formulation

Ingredients	Weight/ Tablet (Mg)
Opadry™ White YS-1-7003	4.38
Antifoam AF Emulsion	0.07
Sureteric YAE-6-18107	16.06
Purified Water USP	
Opadry™ Clear YS-1-7472	0.73

Total coated tablet weight 167.24 mg.

The rapid onset formulation of the previous example has exhibited in-vitro dissolution profiles as shown in Table 6 below, when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm. The numerical values are expressed as percentages of dissolved active ingredient.

Table 6: Dissolution profiles:

Pyridoxine HCl:	Run 1	Run 2	Run3	Run 4	Run 5	Run 6	Avg.
15 minutes	17	13	25	31	17	22	21
30 minutes	31	28	60	63	36	43	43
45 minutes	51	45	78	80	55	60	61
60 minutes	69	64	88	89	67	72	75
75 minutes	79	76	94	94	77	81	83
90 minutes	84	84	97	97	83	87	89
105 minutes	88	89	98	99	87	90	92
120 minutes	91	93	98	98	89	92	93
Doxylamine Succinate	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Avg.
15 minutes	16	14	22	31	47	61	32
30 minutes	31	27	64	63	38	40	44
45 minutes	47	44	75	79	58	61	61
60 minutes	71	61	90	85	68	74	75
75 minutes	76	71	96	89	81	82	82
90 minutes	85	80	101	88	83	81	86
105 minutes	92	86	103	95	93	92	93
120 minutes	93	88	101	96	96	95	95

It follows from these results that the novel formulation demonstrates a rapid onset as shown by its dissolution profile. Pyridoxine HCl presents an average dissolution profile of over 90% within 120 minutes of starting the measurements. Similarly, Doxylamine succinate displays an average dissolution profile of over 90% within 120 minutes of starting the measurements.

Example 3 (Comparative example using prior art formulation)

The following is an example of the prior art Diclectin formulation. An example for a 146.2 mg tablet is provided. This example demonstrates a strikingly slower onset of dissolution in comparison to the present invention.

Table 7: Core Ingredients:

Ingredients	Weight Mg/Tab.	Weight % / Tab.
Pyridoxine HCl	11.0	7.5
Doxylamine Succinate	10.2	7.0
Lactose NF	25.0	17.1
Microcrystalline Cellulose NF	65.0	44.4
Magnesium Trisilicate	30.0	20.6
Silicon Dioxide	1.0	0.7
Magnesium Stearate	4.0	2.7
Total:	146.2	100

The coating formulation is as follows:

Table 8: Coating Formulation

Ingredients
Coating Solution No. 714
Coating Powder No. 303
C.A.P. solution 10%
C.A.P. solution 5%
Gelatin Solution No. 105
Dusting Powder No. 755
White Smoothing Syrup
Sugar Syrup No. 111
Opalux AS-7000-B white
Wax Solution No. 723

The current formulation of the previous example has exhibited in-vitro dissolution profiles as shown in Table 9 below, when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm. The numerical values are expressed as percentages of dissolved active ingredient.

Table 9: Dissolution profiles:

Pyridoxine HCl:	Run 1	Run 2	Run3	Run 4	Run 5	Run 6	Avg.
15 minutes	9	11	18	11	16	12	13
30 minutes	22	23	32	25	28	23	25
45 minutes	37	34	45	39	42	34	38
60 minutes	50	44	56	49	51	44	49
90 minutes	69	63	73	69	67	63	67
120 minutes	83	76	84	82	80	76	80
150 minutes	94	86	91	91	86	86	89
180 minutes	99	94	98	96	93	92	95
240 minutes	93	93	100	100	99	101	98
Doxylamine Succinate	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Avg.
15 minutes	12	15	17	8	18	16	14
30 minutes	17	21	31	18	27	30	24
45 minutes	24	32	45	25	38	38	34
60 minutes	34	41	56	36	46	49	44
90 minutes	52	55	69	55	62	66	60
120 minutes	69	65	75	68	71	75	71
150 minutes	80	74	80	78	79	82	79
180 minutes	82	78	86	82	80	84	82
240 minutes	95	89	89	82	80	87	87

It follows from these results that the prior art formulation, exhibits a noticeably slower dissolution pattern when compared with the novel formulations. Indeed, after 90 minutes averages of only 60% doxylamine and 67% pyridoxine HCl are dissolved. A slower in-vivo dissolution profile is indicative of a delayed onset of action. The novel formulations, as depicted by examples 1 and 2, show markedly faster onset dissolution

profiles resulting in a rapid onset of action. The new formulations overcome most, if not all of the drawbacks associated with the prior art.

The terms and descriptions used herein are preferred embodiments set forth by way of illustration only, and are not intended as limitations on the many variations which those of skill in the art will recognize to be possible in practicing the present invention. It is the intention that all variants whether presently known or unknown, that do not have a direct effect upon the way the invention works, are to be covered by the following claims.

CLAIMS

1. An enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation comprising a disintegrating agent such that the following dissolution profiles are satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

   (a) at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 30 minutes of measurement;

   (b) at least about 70% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 60 minutes of measurement;

   (c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 90 minutes of measurement;

   (d) at least about 90% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 120 minutes of measurement.

2. An enterically-coated pyridoxine HCl and doxylamine succinate rapid onset formulation as in claim 1, wherein the following dissolution characteristics are also satisfied when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm:

   (a) at least about 20% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 15 minutes of measurement;

(b) at least about 60% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 45 minutes of measurement;

(c) at least about 80% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved after 75 minutes of measurement.

3. The rapid onset formulation of claims 1 or 2, wherein at least about 40% of the total amounts of each of pyridoxine HCl and doxylamine succinate are dissolved within 5 minutes when measured in 1000 ml phosphate buffer at pH 6.8 and 37°C in a type 2 dissolution apparatus at 100 rpm.

4. The rapid onset formulation of claims 1 or 2, wherein said formulation contains a core coated with at least one enteric coating, said core comprising pyridoxine HCl, doxylamine succinate and the following non-active excipients: a filler or binder, a disintegrating agent, a lubricant, a silica flow conditioner and a stabilizing agent.

5. The rapid onset formulation of claim 4, wherein said filler or binder consists of microcrystalline cellulose.

6. The rapid onset formulation of claim 4, wherein said disintegrating agent consists of sodium crosscarmellose.

7. The rapid onset formulation of claim 4, wherein said lubricant consists of magnesium stearate.

8. The rapid onset formulation of claim 4, wherein said silica flow conditioner consists of silicon dioxide.

9. The rapid onset formulation of claim 4, wherein said stabilizing agent consists of magnesium trisilicate.

10. The rapid onset formulation of claims 1 or 2, wherein said core comprises:

(a) about 4-10% by weight of pyridoxine HCl;

(b) about 4-10% by weight of doxylamine succinate;

(c) about 40-80% by weight of microcrystalline cellulose;

(d) about 10-30% by weight of magnesium trisilicate;

(e) about 0.5-5% by weight of silicon dioxide;

(f) about 0.5-5% by weight of sodium croscarmellose; and

(g) about 0.5-5% by weight of magnesium stearate.

11. The rapid onset formulation of claim 10, wherein said core comprises:

(a) about 7% by weight of pyridoxine HCl;

(b) about 7% by weight of doxylamine succinate;

(c) about 62% by weight of microcrystalline cellulose;

(d) about 18% by weight of magnesium trisilicate;

(e) about 0.7% by weight of silicon dioxide;

(f) about 2.5% by weight of sodium croscarmellose; and

(g) about 2.8% by weight of magnesium stearate.

12. The rapid onset formulation of claim 4, wherein said at least one enteric coating is aqueous based.

13. The rapid onset formulation of claim 12, wherein said enteric coating consists of a seal coat applied to the core, an enteric coating *per se* applied on the seal coat and an aesthetic top coat applied on the enteric coating *per se*.

14. Use of the rapid onset formulation of claims 1 or 2 in the preparation of a medicament for treating nausea and vomiting in a patient in need thereof.

15. Use of the rapid onset formulation of claims 1 or 2 in the preparation of a medicament for treating nausea and vomiting during pregnancy in a patient in need thereof.

16. A medicament for attenuating the symptoms associated with nausea and vomiting consisting essentially of the formulation of claim 4.

17. A process for preparing the rapid onset formulation of claim 4, said process comprising the steps of:

- blending said doxylamine succinate and said silica flow conditioner to obtain a pre-blend;
- mixing said preblend with said pyridoxine HCl to obtain an active ingredient blend;
- mixing said active ingredient blend with said remaining non-active excipients, namely: a filler or binder, a disintegrating agent, a lubricant, and a stabilizing agent to obtain a final blend; and
- tabletting and coating said final blend.

18. A process in accordance with claim 17 wherein said final tabletting and coating step comprises compression of said final into a tablet shape, seal coating of said tablet shape, followed by enteric coating, followed by colour coating.