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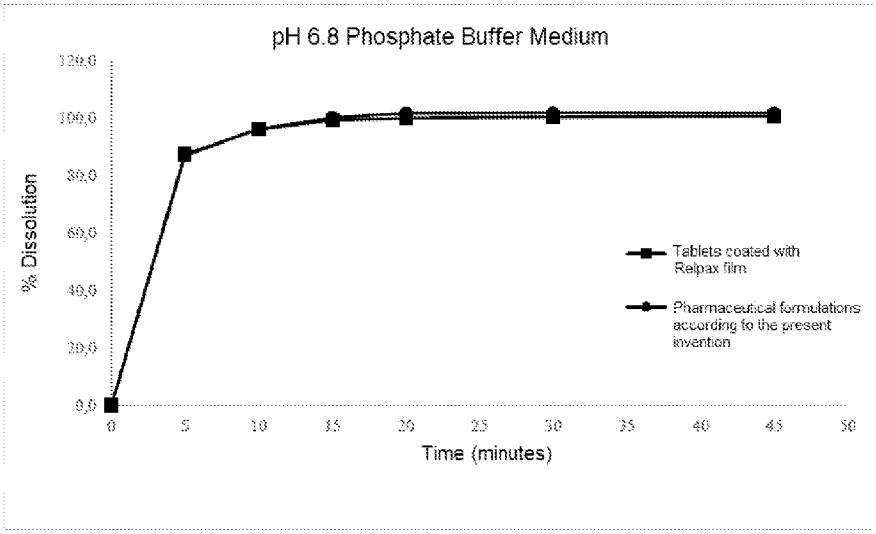

Figure 3

(57) Abstract: The present invention relates to orodispersible film formulations comprising high amounts of eletriptan or pharmaceutically acceptable salt thereof and use of these formulations in the treatment of migraine.

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ORODISPERSIBLE FILM FORMULATIONS COMPRISING HIGH DOSES OF ELETRIPTAN

The Related Technical Field

The present invention relates to orodispersible film formulations comprising high amounts of eletriptan or pharmaceutically acceptable salt thereof, and use of these formulations in the treatment of migraine.

State of the Art

Migraine is a very common disease that progresses with an average of two attacks per month, is usually one-sided, worsens with physical activity and is characterized by attacks associated with moderate-to-severe throbbing headache, nausea and/or vomiting, photophobia and phonophobia. The vast majority of people having migraine use an anti-migraine drug as an acute treatment method. The object of the treatment of acute migraine attack is to quickly alleviate the pain and associated symptoms, and to prevent the recurrence of the pain.

Acute treatment is gaining importance since in migraine attacks the pain that cannot be relieved within 60 – 120 minutes might cause central sensitization and allodynia (*Burstein R, Jakubowski M, Rauch SD. The science of migraine. J Vestib Res 2011;21(6):305–14*).

Drugs used in the treatment of attacks can be divided into two main groups, namely non-specific and specific migraine drugs. Non-specific drugs include simple analgesics, combination analgesics (analgesics comprising caffeine or codeine combinations), NSAIDs, neuroleptic drugs, antiemetic drugs, steroids, and opioids. Specific drugs are divided into two groups, namely drugs belonging to ergo group (drugs containing ergotamine tartrate) and belonging to triptan group.

Triptans, which are the most recently discovered molecular group of migraine-specific drugs, are free from the side effects of ergotamine narrowing the peripheral vessels, as they have agonistic actions selective to 5-HT 1B/1D receptors. They also have very

high absorption rates compared to ergotamine, which has very low absorption rates. This creates an opportunity to easily administer effective doses.

Eletriptan is a serotonin agonist used in the treatment of acute migraine headache. It is a member of a group of anti-migraine drugs comprising almotriptan, frovatriptan, naratriptan, rizatriptan, and sumatriptan which are commonly called "triptans". It is a selective 5-HT1 receptor agonist with a structure as shown in the figure below; its chemical name is (R)-3-(1-methyl-2-pyrrolidinylmethyl)-5-[2-(phenylsulfonyl)ethyl]-1H-indole.

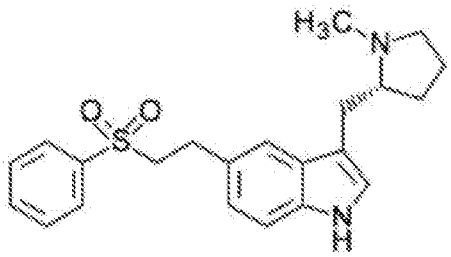

Figure. 1

In a clinical trial comparing oral eletriptan and sumatriptan, it was found that 80 mg of eletriptan was superior to 100 mg of sumatriptan in terms of onset of action, remission response rate to headache, painless remission response rate, and amelioration of the symptoms associated with migraine. Better oral bioavailability and longer half-life are other advantages of eletriptan over sumatriptan.

Eletriptan was licensed by the FDA in 2002 in oral tablet form in 20 and 40 mg doses with the trade name Relpax®, for use in the treatment of migraine with or without aura.

Eletriptan was first disclosed in patent document No. EP0592438 B1 for use in the treatment of hypertension, depression, anxiety, eating disorders, obesity, substance abuse, cluster headache, migraine, pain and chronic paroxysmal hemicrania, and vascular disorders associated with headache.

While patent document No. EP0776323 B1 discloses the hydrobromide salt of eletriptan and processes for obtaining hydrobromide salt, patent document No. EP1135381 B1 discloses the hydrobromide monohydrate form of eletriptan.

The technical problem to be solved by the invention

Conventional tablets containing eletriptan existing in the state of the art, are not useful enough for situations where rapid action should be taken.

In conventional tablet or capsule dosage forms, the tablet must be disintegrated or dissolved before the drug enters into the systemic circulation and is absorbed there, and the therapeutic effect occurs. Furthermore, swallowing the tablet or capsule dosage forms comprising high doses of active ingredients poses a major problem for pediatric, geriatric or mentally retarded patients. Liquid dosage forms are not suitable dosage forms since they have a short half-life despite exhibiting a rapid action.

Solid oral dosage forms such as tablets and capsules do not provide sufficient success in the treatment of diseases such as migraine, where the action must be seen quickly (for example, in the first half hour or less).

In order to overcome the disadvantageous dosage forms described above and to provide the most suitable administration route to the patients, there is a need for dosage forms that dissolve quickly, especially for those that disintegrate/dissolve in saliva and do not require water. Hence, orodispersible film formulations have been developed.

Drugs in the form of a orodispersible film are thin films of hydrophilic polymers that resembles postage stamps in size, shape and thickness, and dissolve quickly on the tongue or on the bottom thereof. In the orodispersible films, the film wet with saliva disintegrates within seconds and releases the drug content. With this dosage form both ease of administration is provided, and the desired therapeutic effect can enter the system more quickly. It is also a very useful dosage form for pediatric, geriatric, bedridden or developmentally retarded patients who have difficulty swallowing tablets.

Orodispersible films are one of the dosage forms that are gaining popularity and that have been studied extensively in the literature after orally disintegrating tablets. The use of orodispersible films is gradually increasing with many advantages such as;

- Easy to use without the need for water,
- The rapid onset of the action with the increased dissolution and absorption

of the drug with by rapid distribution in the mouth,

- Allowing higher solubility with a larger surface area compared to orally disintegrating tablets,
- Application at lower doses without the first pass effect, thereby reducing undesirable effects and increasing clinical performance,
- Providing ease of drug administration in many patient groups such as pediatric and geriatric patients, bedridden patients and patients having psychological disorders,
- Being suitable for taste masking,
- Being a more flexible and stable dosage form compared to orally disintegrating tablets.

However, dosage forms of the orodispersible film have very low capacity to carry active ingredients. There is a need for pharmaceutical formulations comprising high doses of eletriptan or a pharmaceutically acceptable salt thereof, which provide a rapid and efficient treatment onset and increase the bioavailability of eletriptan especially in the treatment of migraine attacks.

The present invention discloses pharmaceutical formulations in the form of orodispersible film, comprising high doses of eletriptan or pharmaceutically acceptable salt thereof, production methods of these formulations, and their use in the treatment of migraine attacks.

Description of the Invention

As a result of their studies, the inventors have succeeded in obtaining a formulation in the form of orodispersible film, comprising high doses of eletriptan or a pharmaceutically acceptable salt thereof where the carrying capacity is increased in the orodispersible film forms.

The present invention relates to orodispersible film formulations, comprising high doses of eletriptan or pharmaceutically acceptable salt thereof.

Specifically, the present invention relates to pharmaceutical formulations in the form of orodispersible film, comprising as a high dose, more than 30% by weight of the film

eletriptan or a pharmaceutically acceptable salt thereof based on the film weight.

More specifically, the present invention relates to pharmaceutical formulations in the form of orodispersible film, comprising as a high dose, more than 35% by weight of the film eletriptan or a pharmaceutically acceptable salt thereof based on the film weight.

Another object of the present invention is to provide a method for producing pharmaceutical formulations in the form of orodispersible film, comprising high doses of eletriptan or a pharmaceutically acceptable salt thereof which has a pleasant taste and dissolve rapidly.

By the term "orodispersible film" according to the present invention is meant a single- or multi-layer thin film that is administered orally to the oral mucosa and disintegrates rapidly in the patient's oral cavity. The active ingredient carried in the orodispersible film disintegrates in the oral mucosa and is absorbed therefrom.

Pharmaceutical formulations in the form of orodispersible film according to the present invention comprise high doses of eletriptan or a pharmaceutically acceptable salt thereof.

In pharmaceutical formulations in the form of a orodispersible film according to the present invention, eletriptan can be used in free form or in the form of a pharmaceutically acceptable salt which may be selected from salts of acetate, aspartate, benzoate, besylate, bicarbonate, carbonate, bisulfate, sulfate, borate, citrate, formate, fumarate, hydrochloride, chloride, hydrobromide, hydrobromide iodide, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthalate, nicotinate, nitrate, oxalate, pamoate, phosphate, hydrogen phosphate, dihydrogen phosphate, stearate, succinate, tosylate, trifluoroacetate, aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, lamine, potassium, sodium, tromethamine and zinc. The eletriptan used according to the present invention in the form of a hydrobromide salt.

Pharmaceutical formulations in the form of orodispersible film according to the present

invention may comprise 5 – 300 mg, preferably 10 – 150 mg of eletriptan or pharmaceutically acceptable salt thereof as active ingredient. Preferred orodispersible film formulations of the invention may comprise preferably 20 mg and 40 mg or equivalent amounts of eletriptan or pharmaceutically acceptable salt thereof.

The orodispersible formulations in the form of film of the present invention comprise at least one pharmaceutically acceptable film former.

In the orodispersible films, the physical characteristics and durability of the resulting film vary greatly depending on the type and amount of polymer used as film former. The polymer used should be non-irritating and non-toxic, have good wetting properties, and be cost-effective. Depending on the polymer type used in the formulations, properties of the resulting product such as disintegration time, drug loading capacity, mechanical resistance and brittleness can be controlled. Therefore, the choice of polymer is a critical parameter for orodispersible films.

The film formers that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention can be selected from pullulan, starch, modified starch, sodium alginate, pectin, low-viscosity pectin, gelatin, polymerized resin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, polyvinyl alcohol, polyethylene oxide, polyvinyl pyrrolidone, polyacrylic acid, or combinations thereof.

The weight of the film former to be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be in the range of 20-60% by weight, based on the total film weight of the present composition.

Preferably, the film formers used in the present invention comprise of a combination of modified starch and pullulan. The ratio of modified starch to pullulan used in the present invention can be 1:7 – 1:1, preferably 1:5 – 1:1.

Pharmaceutical formulations in the form of orodispersible film according to the present invention may comprise eletriptan or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient together with at least one

pharmaceutically acceptable film former. Pharmaceutically acceptable excipients that can be used according to the present invention may be selected from plasticizers, surfactants, colorants, flavoring agents, sweeteners, fillers, flavor enhancers, solvents, or combinations thereof.

Plasticizers that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from propylene glycol, polyethylene glycol, low molecular weight polyethylene glycol, glycerin, phthalic acid esters, sorbitol, maltitol, starch syrup, triacetin, or combinations thereof. The amount of plasticizer used in the present invention can be in the range of 0.5 – 20% by weight, based on the total film weight.

Surfactants that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from polysorbate 80, sodium lauryl sulfate, poloxamer, benzalkonium chloride, lecithin, or combinations thereof.

Colorants that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from titanium dioxide, FD&C approved colorants, silicon dioxide, natural juice concentrates, or combinations thereof.

Flavoring agents that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from resins, extracts and/or oils obtained from fruits such as peppermint oil, thyme oil, laurel oil, coconut oil, sage oil, almond oil, and synthetic flavors such as mint flavor, lemon flavor, orange flavor, grape flavor, linden flavor, strawberry flavor, chocolate flavor, vanilla flavor.

Natural or artificial sweeteners can be used to increase patient compliance and to mask bitter taste in orodispersible film formulations. Sweeteners that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from glucose, sucrose, dextrose, fructose, maltose, aspartame, saccharin, sucralose, acesulfame-K, or combinations thereof. The amount

of sweetener used in the present invention is 2 – 10% (w/w) by weight, based on the total film weight.

Fillers that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from pullulan, mannitol, microcrystalline cellulose, cellulose polymers, magnesium carbonate, calcium carbonate, silicate, talc, or combinations thereof.

The flavor enhancers that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from neohesperidin dihydrochalcone, mannitol, maltose, fructose, galactooligosaccharide, dextrin, lactose, glucose, sorbitol, xylitol, sucralose, or combinations thereof.

Solvents that can be used in the pharmaceutical formulations in the form of orodispersible film according to the present invention may be selected from ethanol, deionized water, isopropanol, methylene chloride, toluene, or combinations thereof.

Another object of the present invention is to describe a method for producing pharmaceutical formulations in the form of orodispersible film, comprising high doses of eletriptan or a pharmaceutically acceptable salt thereof.

Pharmaceutical formulations in the form of orodispersible film according to the present invention can be obtained by a production method that may be selected from solvent casting method, hot melt extrusion method, semi-solid molding method, rolling method, solid dispersion methods. Preferably, orodispersible film according to the present invention is produced using the solvent casting method.

Solvent casting technique is frequently preferred since it is an easy technique in the production of orodispersible films, is not expensive, does not require high temperatures and special requirements. In this method, after the aqueous or hydro-alcoholic solution of the active ingredients and auxiliary substances is prepared, air bubbles are removed by means of vacuum. Then it is poured onto the surface as a flat layer, dried and cut into desired dimensions to obtain a film with a uniform thickness.

Pharmaceutical formulations in the form of orodispersible film according to the present invention can be produced by a production method according to the following steps;

- Adding slowly and mixing continuously eletriptan or pharmaceutically acceptable salt thereof and at least one film former and preferably at least one excipient until a homogeneous suspension is formed,
- Pouring the resulting mixture onto a hydrophobic film and subjecting it to a coating process and subsequently drying it,
- Cutting the resulting films into desired dimensions, and packaging.

During the production of the orodispersible films according to the present invention, the resulting mixture can preferably be subjected to a defoaming process before being poured onto a hydrophobic film.

More particularly, pharmaceutical formulations in the form of orodispersible film according to the present invention can be produced by a production method comprising the following steps;

- Adding slowly and mixing continuously eletriptan or pharmaceutically acceptable salt thereof and at least one film former until a homogeneous suspension is formed,
- Preferably, at least one pharmaceutically acceptable excipient is slowly added to the mixture and mixed continuously,
- Starting the defoaming process and repeating it until the product reaches the desired viscosity,
- Pouring the resulting mixture onto a hydrophobic film and subjecting it to a coating process and subsequently drying it,
- Cutting the resulting films into desired dimensions, and packaging.

The hydrophobic film used in the production method of pharmaceutical formulations in the form of orodispersible films according to the present invention may be siliconized polyester (PET) film conventionally used during the production of orodispersible films.

In the production method of pharmaceutical formulations in the form of

orodispersible film according to the present invention, the drying process can be carried out at a temperature between 50°C – 150°C.

The orodispersible film according to the present invention may have a thickness of 50 – 300 µm, preferably 50 – 150 µm, and a weight of 5 – 500 mg, more preferably 10 – 150 mg.

The orodispersible film according to the present invention may have a size of 1 – 10 cm^2, preferably the resulting orodispersible film has a size of 2.5 – 8 cm^2. Additionally, the orodispersible films according to the present invention may be rectangular, square, circular, or an ellipse in shape, preferably resulting orodispersible films are rectangular in shape.

The disintegration or dissolution of the orodispersible film according to the present invention once it is placed in the oral cavity depends on its contact with saliva, and the film disintegrates in less than 2 minutes, preferably less than 1 minute, and more preferably less than 45 seconds.

The particle size of the active ingredient used in pharmaceutical formulations in the form of orodispersible film is a critical parameter in the production stage. Accordingly, eletriptan or pharmaceutically acceptable salt thereof used in the orodispersible film according to the present invention has a D90 particle size value which is below 60 µm. As used herein, the term "particle size" refers to the volume diameter of particles, as measured by the laser diffraction method using a Malvern Mastersizer 2000. The D90 value represents the particle size by volume of 90% of the particles.

During the production of pharmaceutical formulations in the form of orodispersible film, if the moisture content is outside a certain range the resulting film is either too brittle or too sticky. Accordingly, during the coating of orodispersible film formulations according to the present invention the moisture content is 5 – 10%.

Viscosity is another critical parameter to be considered in pharmaceutical formulations in the form of orodispersible film. Problems arise during the production of the film if

the viscosity of the resulting mixture is too low or too high, preferably the viscosity of the orodispersible films according to the present invention is 7000 – 14000 cps.

Industrial Applicability of the Invention

Pharmaceutical formulations in the form of orodispersible film according to the present invention can appeal to a wide range of patient profiles. It is suitable for use by all patient groups, particularly those who have difficulty in swallowing, such as pediatric and geriatric patients. Moreover, orodispersible films are preferred dosage forms due to their rapid disintegration and effectiveness in the treatment of diseases such as migraine and headache, where taking rapid action is critical.

Also, pharmaceutical formulations in the form of orodispersible film according to the present invention are characterized by comprising high amounts of eletriptan or pharmaceutically acceptable salt thereof. Thus, pharmaceutical formulations comprising high doses of eletriptan or a pharmaceutically acceptable salt thereof are obtained, which provide a rapid and efficient treatment onset and increase the bioavailability of eletriptan.

Pharmaceutical formulations in the form of orodispersible film according to the present invention can be used in the treatment of cluster headaches, migraine, pain and chronic paroxysmal hemicrania, and vascular disorders associated with headache.

Examples

The following examples are given in order that the subject of the invention can be more fully understood, and these cannot be used to limit the subject of the invention in any way.

Preparation of orodispersible film formulations

Orodispersible film formulations comprising eletriptan hydrobromide were prepared according to the compounds shown in Table 1 below and their amounts in the unit formulation.

Table. 1 – Compositions of orodispersible film formulations comprising eletriptan hydrobromide

	Example 1 – 40		**Example 2 – 40**		**Example 3 – 20**	
	mg	**%**	**mg**	**%**	**mg**	**%**
Eletriptan Hidrobromid	48,46	51,03	48,46	43,91	24,23	43,91
Plasticizer	0,00	0,00	10,00	9,06	5,00	9,06
Plasticizer	3,50	3,69	3,00	2,72	1,50	2,72
Surfactant	1,50	1,58	0,50	0,45	0,25	0,45
Filler	6,20	6,53	0,00	0,00	0,00	0,00
Colorant	0,50	0,53	0,30	0,27	0,15	0,27
Film Former	15,90	16,74	11,90	10,78	5,95	10,78
Flavoring Agent	0,20	0,21	0,20	0,18	0,10	0,18
Colorant	5,00	5,27	5,00	4,53	2,50	4,53
Film Former	17,10	18,01	30,00	27,18	15,00	27,18
Sweetening Agent	1,60	1,68	6,00	5,44	3,00	5,44
Ethanol	60,00	-	60,00	-	30,00	-
Deionized Water	90,00	-	90,00	-	45,00	-
Solid Content Strips	**94,96**	**100,00**	**110,36**	**100,00**	**55,18**	**100,00**

In the example formulations, the compositions of which are given above, ethanol, polysorbate 80, polyethylene glycol 200 and glycerin are firstly placed into the production vessel and mixed. To the mixture, titanium dioxide, deionized water, and sucralose are slowly added, and the mixing is continued. Eletriptan hydrobromide is slowly added and mixed, and to this, FD&C Red solution, modified starch, pullulan and strawberry flavoring are added and the mixing is continued. The homogeneity of the mixture is checked. The resulting mixture is subjected to defoaming process, and until it is free of foam this process is continued.

Once the defoaming is complete, the resulting mixture is poured onto the siliconized PET film as a flat layer and subsequently subjected to drying with hot air. The films that reach the target thickness and weight are cut into the desired dimensions, and packaged.

Experimental Studies

Dissolution Results

It was found that the formulations of Example 2 and Example 3 exhibited very good results when the pharmaceutical formulations according to the present invention were prepared based on the unit formulas in Table.1 above. Accordingly, the comparative dissolution tests of Example 2 with the reference Relpax® tablet product are shown in Tables 2 – 4 below.

Table.2 – In 0.1 N HCl medium

Time (min)	**5**	**10**	**15**	**20**	**30**	**45**
Relpax ®	93,5	101,2	102,7	102,9	103,1	103,1
Example 2	90,4	96,3	96,8	95,8	96,6	97,2

Table.3 – In pH 4.5 Acetate Buffer Medium

Time (min)	**5**	**10**	**15**	**20**	**30**	**45**
Relpax ®	89,5	97,6	100,2	101,4	102,0	102,3
Example 2	84,0	96,3	99,4	100,2	100,6	100,8

Table.4 – In pH 6.8 Phosphate Buffer Medium

Time (min)	**5**	**10**	**15**	**20**	**30**	**45**
Relpax ®	87,5	96,1	99,3	100,1	100,5	100,8
Example 2	87,0	96,2	100,3	101,7	101,9	101,8

Physical characteristics

The orodispersible films according to the present invention were prepared based on the unit formulas in Table.5 above, and the resulting films were compared in terms of their physical characteristics.

Table.5 Comparative table of physical characteristics of orodispersible films

Physical characteristics	**Example 1**	**Example 2**	**Example 3**
Weight (mg/7.5 cm2)	94,96	110,36	55,18
Thickness (µm)	120	120	120

Disintegration time	40”	30”	32”
Average dissolution in 0.1 N HCl medium (%)	95.8	96.8	96.3
Taste	Bitter	Sweet	Sweet

Stability Tests

For the orodispersible film formulations comprising eletriptan or pharmaceutically acceptable salt thereof according to the present invention, stability studies have been carried out at three different temperature and humidity values (25°C 60% RH, 30°C 75% RH, 40°C 75% RH) for three months, and the results obtained are given in the Table 6 below.

Table.6 Comparative stability table of orodispersible film formulations

	Example 2 25°C	**Example 2 30°C**	**Example 2 40°C**	**Example 3 25°C**	**Example 3 30°C**	**Example 3 40°C**
Dissolution Rate	97.63	100.43	97.51	97.51	99.82	96.98
Quantitation	99.12	98.56	98.98	98.93	98.01	97.89
Related Compounds						
Eletriptan N-Oxide	Below LOQ*	Below LOQ*	Below LOQ*	Below LOQ*	Below LOQ*	Below LOQ*
Eletriptan Dimer	Below LOQ*	Below LOQ*	Below LOQ*	Below LOQ*	Below LOQ*	Below LOQ*
Each Unknown Impurity	0.07	0.07	0.09	0.06	0.07	0.07
Total Impurity	0.13	0.15	0.20	0.14	0.17	0.18
Isomeric Impurity	ND*	ND*	ND*	ND*	ND*	ND*

*Below LOQ: Below the limit of quantitation / *ND: Not detected

The formulations prepared in Example 2 and Example 3 showed a similar dissolution profile with the reference tablet product in the state of the art, were able to disintegrate in less than 1 minute during a migraine attack, showed a rapid action, and became user-

friendly with a pleasant taste when the data for the formulations prepared within the present invention are compared.

Description of the Drawings

Figure 1. Comparative dissolution plot in 0.1 N HCl Medium

Figure 2. Comparative dissolution plot in pH 4.5 Acetate Buffer Medium

Figure 3. Comparative dissolution plot in pH 6.8 Phosphate Buffer Medium

CLAIMS

1. Orodispersible film formulation comprising eletriptan or a pharmaceutically acceptable salt thereof as an active ingredient, wherein the amount of eletriptan or pharmaceutically acceptable salt thereof is more than 30% by weight, based on the film weight.

2. Orodispersible film formulation according to claim 1, wherein the amount of eletriptan or pharmaceutically acceptable salt thereof as an active ingredient is more than 35% by weight, based on the film weight.

3. Orodispersible film formulation according to any of the preceding claims, wherein the pharmaceutically acceptable salt of eletriptan is selected from salts of acetate, aspartate, benzoate, besylate, bicarbonate, carbonate, bisulfate, sulfate, borate, citrate, formate, fumarate, hydrochloride, chloride, hydrobromide, hydrobromide iodide, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthalate, nicotinate, nitrate, oxalate, pamoate, phosphate, hydrogen phosphate, dihydrogen phosphate, stearate, succinate, tosylate, trifluoroacetate, aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, lamine, potassium, sodium, tromethamine and zinc.

4. Orodispersible film formulation according to claim 3, wherein the pharmaceutically acceptable salt of eletriptan is hydrobromide salt.

5. Orodispersible film formulation according to any of the preceding claims, wherein the amount of eletriptan or pharmaceutically acceptable salt thereof is 5 – 300 mg.

6. Orodispersible film formulation according to claim 5, wherein the amount of eletriptan or pharmaceutically acceptable salt thereof is 10 – 150 mg.

7. Orodispersible film formulation according to claim 6, wherein the amount of

eletriptan or pharmaceutically acceptable salt thereof is 20 mg.

8. Orodispersible film formulation according to claim 6, wherein the amount of eletriptan or pharmaceutically acceptable salt thereof is 40 mg.

9. Orodispersible film formulation according to any of the preceding claims, comprising at least one pharmaceutically acceptable film former.

10. Orodispersible film formulation according to claim 9, wherein the weight of the pharmaceutically acceptable film former is 20 – 60% by weight, based on the total film weight.

11. Orodispersible film formulation according to any of claims 9-10, wherein the pharmaceutically acceptable film former is selected from pullulan, starch, modified starch, sodium alginate, pectin, low-viscosity pectin, gelatin, polymerized resin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, polyvinyl alcohol, polyethylene oxide, polyvinyl pyrrolidone, polyacrylic acid, or combinations thereof.

12. Orodispersible film formulation according to claim 11, wherein the pharmaceutically acceptable film former consists of a combination of modified starch and pullulan.

13. Orodispersible film formulation according to claim 12, wherein the ratio of modified starch to pullulan is 1:7 – 1:1.

14. Orodispersible film formulation according to any of claims 12-13, wherein the ratio of modified starch to pullulan is 1:5 – 1:1.

15. Orodispersible film formulation according to any of the preceding claims, comprising at least one pharmaceutically acceptable excipient.

16. Orodispersible film formulation according to claim 15, wherein the pharmaceutically acceptable excipient is selected from plasticizers, surfactants, colorants, flavoring agents, sweeteners, fillers, flavor enhancers, solvents or combinations thereof.

17. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable plasticizer is selected from propylene glycol, polyethylene glycol, low molecular weight polyethylene glycol, glycerin, phthalic acid esters, sorbitol, maltitol, starch syrup, triacetin or combinations thereof.

18. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable surfactant is selected from polysorbate 80, sodium lauryl sulfate, poloxamer, benzalkonium chloride, lecithin or combinations thereof.

19. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable colorant is selected from titanium dioxide, FD&C approved colorants, silicon dioxide, natural juice concentrates, or combinations thereof.

20. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable flavoring agent is selected from resins, extracts and/or oils obtained from fruits such as peppermint oil, thyme oil, laurel oil, coconut oil, sage oil, almond oil, and synthetic flavors such as mint flavor, lemon flavor, orange flavor, grape flavor, linden flavor, strawberry flavor, chocolate flavor, vanilla flavor.

21. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable sweetener is selected from glucose, sucrose, dextrose, fructose, maltose, aspartame, saccharin, sucralose, acesulfame-K, or

combinations thereof.

22. Orodispersible film formulation according to claim 21, wherein the amount of sweetener is 2 – 10% by weight, based on the total film weight.

23. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable filler is selected from pullulan, mannitol, microcrystalline cellulose, cellulose polymers, magnesium carbonate, calcium carbonate, silicate, talc, or combinations thereof.

24. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable flavor enhancer is selected from neohesperidin dihydrochalcone, mannitol, maltose, fructose, galactooligosaccharide, dextrin, lactose, glucose, sorbitol, xylitol, sucralose, or combinations thereof.

25. Orodispersible film formulation according to claim 16, wherein the pharmaceutically acceptable solvent is selected from ethanol, deionized water, isopropanol, methylene chloride, toluene, or combinations thereof.

26. Orodispersible film formulation according to any of the preceding claims, wherein it is produced by a production method consisting of the following steps;
    - Adding slowly and mixing continuously eletriptan or pharmaceutically acceptable salt thereof and at least one film former and preferably at least one excipient until a homogeneous suspension is formed,
    - Pouring the resulting mixture onto a hydrophobic film and subjecting it to a coating process and subsequently drying it,
    - Cutting the resulting films into desired dimensions, and packaging.

27. Orodispersible film formulation comprising eletriptan or a pharmaceutically acceptable salt thereof as an active ingredient according to any of the preceding claims, for use in the treatment of cluster headaches, migraine, pain and chronic paroxysmal hemicrania, and vascular disorders associated with headache.

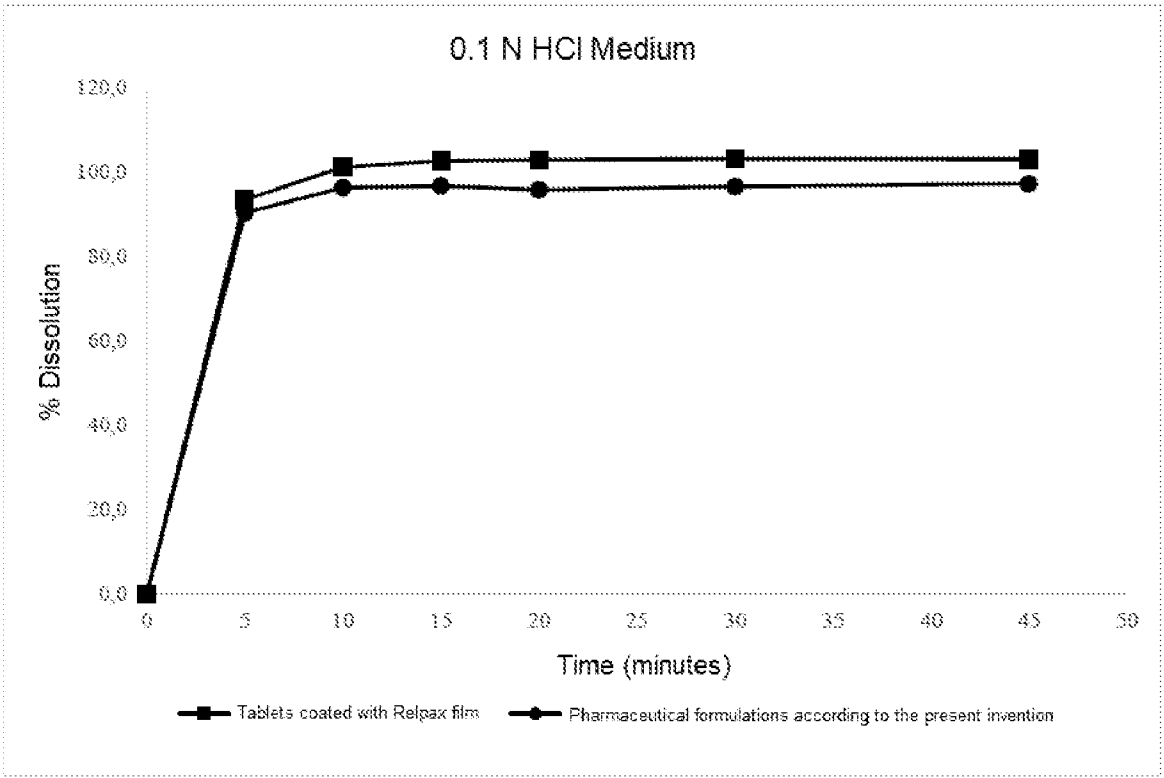

Figure 1

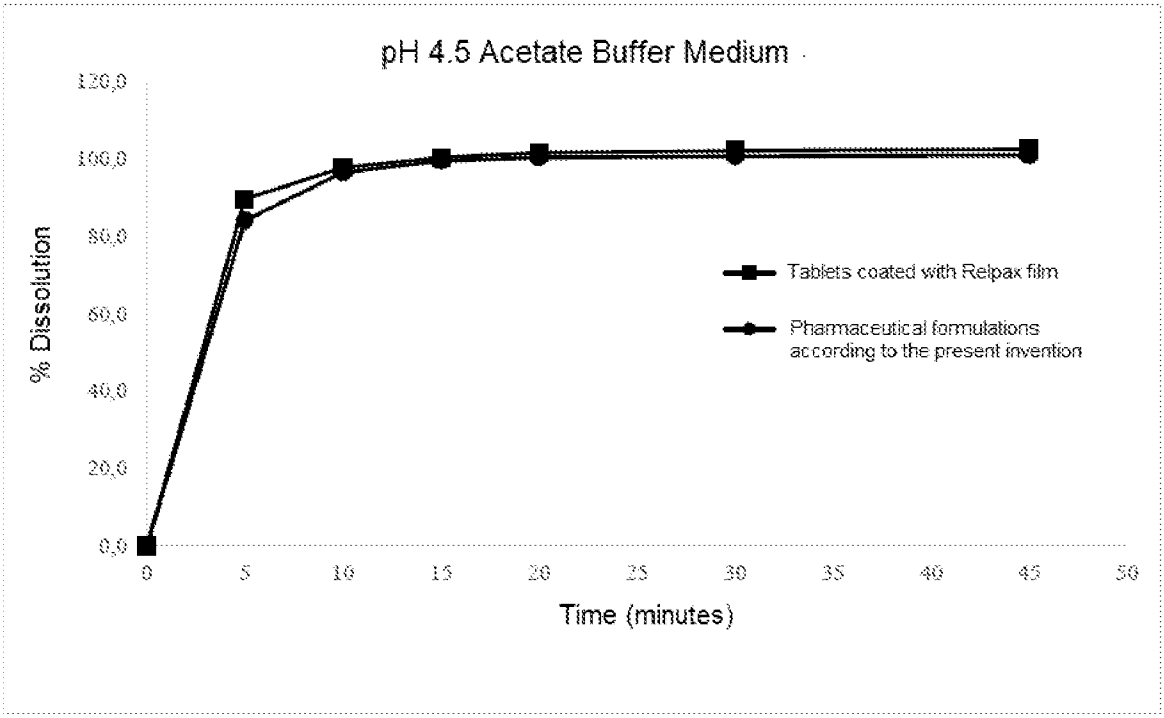

Figure 2

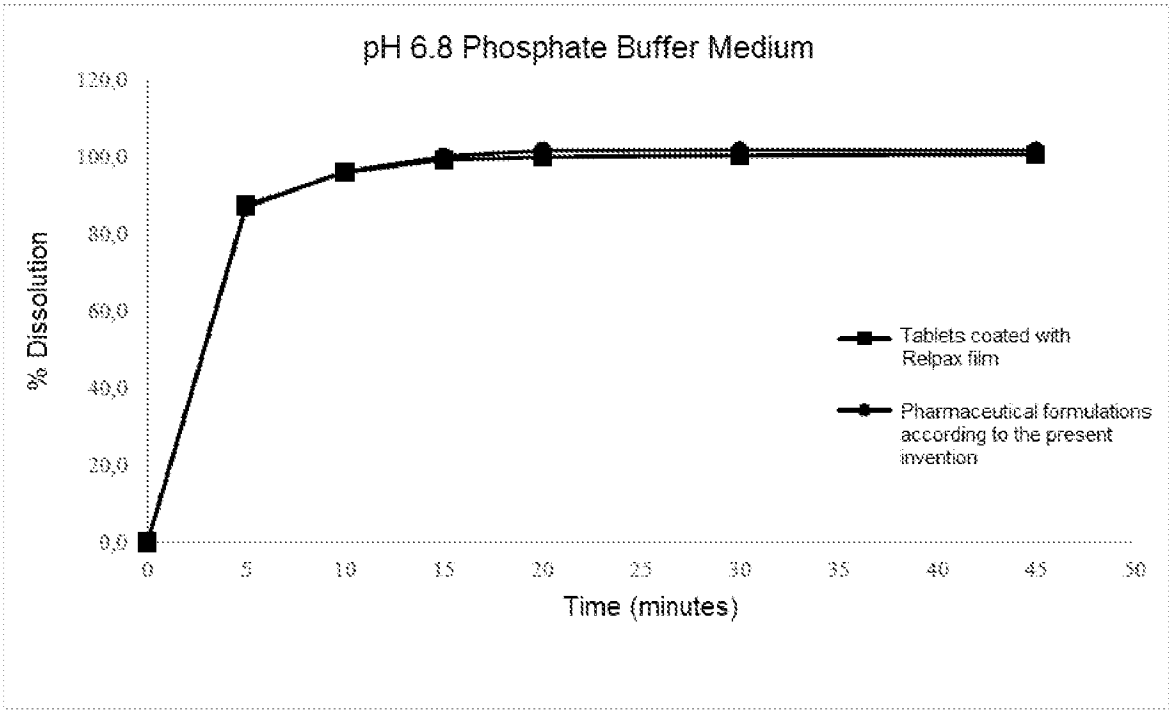
pH 6.8 Phosphate Buffer Medium
% Dissolution
120,0
100,0
80,0
60,0
40,0
20,0
0,0
0
5
10
15
20
25
30
35
40
45
50
Time (minutes)
Tablets coated with Relpax film
Pharmaceutical formulations according to the present invention

Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2021/050624

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/404 (2006.01)i; A61K 9/70 (2006.01)i; A61P 25/06 (2006.01)i

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)

A61K; A61P

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 practicable, search terms used)

EPODOC, Google Scholar, PubMed, Science Direct

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Kothapuvari, Pavan Kumar, Swati Rawat, and D. V. R. N. Bhikshapathi. "Preparation, optimization and in vivo evaluation of eletriptan hbr fast dissolving oral films." Int J Drug Deliv 7 (2015): 141-54. Abstract; titles “Preparation of Eletriptan Hydrobromide Films”, “Results and discussion-Preparation of Eletriptan Hydrobromide films”, “Summary and conclusion”; Tables 1-3	1-7, 9-27 8
X	Pallavi, K., and T. Pallavi. "Formulation and evaluation of fast dissolving films of eletriptan hydrobromide." International Journal of Current Pharmaceutical Research 9.2 (2017): 59. Abstract; titles “Materials and Methods”, “Results and Discussion”; Tables 1-2	1-7, 9, 11, 15-17, 23-27
Y	Palve, Swapnil, et al. "Oral Dispersible Film Containing Eletriptan Hydrobromide for Treatment of Migraine: Design, Formulation, Evaluation and Optimization." International Journal of Pharmaceutical Research 11.4 (2019). Abstract; page 271, column 2; title “Preparation of drug-loaded film”	8

☑ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
“A” document defining the general state of the art which is not considered to be of particular relevance
“D” document cited by the applicant in the international application
“E” earlier application or patent 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	Date of mailing of the international search report
30 November 2021	**30 November 2021**

Name and mailing address of the ISA/TR	Authorized officer
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Somwanshi, Shrushti V., and Sanjay S. Thonte. "Formulation Development and in vitro Evaluation of Eletriptan Fast Dissolving Oral Films." International Journal of Pharmaceutical Sciences and Drug Research 10.6 (2018): 447-453. Abstract; title “Preparation of Eletriptan Mouth Dissolving Films”; Tables 1-3	1-27