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(54) Title: PHARMACEUTICAL COMPOSITION OF FURAZIDIN FOR VAGINAL ADMINISTRATION

(57) Abstract: A pharmaceutical composition of furazidin in the form of a vaginal mucoadhesive tablet, said tablet comprising or consisting of: a) a granulate containing furazidin, a pharmaceutically acceptable polymeric mucoadhesive binder, and intragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more intragranular fillers and an intragranular disintegrant; and b) extragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more extragranular fillers, an extragranular disintegrant, and a lubricant, and wherein the tablet comprises from 1 to 15% by weight of furazidin with respect to the weight of the tablet.



PHARMACEUTICAL COMPOSITION OF FURAZIDIN FOR VAGINAL ADMINISTRATION

5 Field of the invention

The invention relates to a pharmaceutical composition comprising furazidin in the form of a tablet for vaginal administration and a process of its preparation. The composition can find use in the local treatment of bacterial vaginitis.

Prior art

10 Furazidin (Furagin, 1-[3-(5-nitro-2-furyl)-2-propenylideneamino-imidazolidine-2,4-dione) is a medicament widely used in the oral treatment of acute and chronic bacterial urinary tract infections (UTI), prostate infections, recurrent urinary tract infections, after surgery of the urinary tract, and prostate inflammation. Pharmaceutical dosage forms for oral administration are tablets, liquid suspensions,
15 and powders or granulates for preparing liquid suspensions. Various furazidin tablets designed for oral administration are present on the market.

WO2022157357 discloses prolonged-release pharmaceutical composition of furazidin for oral administration in the treatment of urinary tract infections (UTI). The prolonged-release pharmaceutical composition for oral administration comprises: a)
20 an immediate release component, comprising furazidin and one or more pharmaceutically acceptable excipients; and b) a modified-release component, comprising furazidin, a controlled-release agent, and one or more pharmaceutically acceptable excipients. In exemplary embodiments tablets have high furazidin content, about 32% to 50% by weight in the immediate release component, and about
25 40 to 60% by weight in the modified-release component.

WO2018069804 discloses in Examples 9 to 15 certain solid pharmaceutical furazidin compositions in the form of a powder or granulate or coated granulate for oral administration in the treatment of urinary tract infections as a suspension or as a

capsule filling, containing from 0.5% to 95% by weight of furazidin, from 5% to 99% by weight of a bulking agent, and 0.1% to 30% by weight of a binder.

Solid oral forms disclosed in WO2018069804 are all multi-unit dosage forms designed specifically for oral administration to patients having difficulties with swallowing, like children and elderly patients, to improve patients compliance. There is no mention whatsoever of the treatment of bacterial vaginitis using furazidin composition, in particular of the treatment of bacterial vaginitis by intravaginal therapy with furazidin composition, let alone any mention of the problem of design of tablets that could be suitable for intravaginal administration in such a treatment.

- 10 A granulate designed for the preparation of mini-tablets to be used as a capsule filling was disclosed in Examples 9 and 15 of WO2018069804. Granulates proposed for compressing into oral mini-tablets include very high weight percentage of furazidin, do not include mucoadhesive polymers and do not include disintegrants, and the mini-tablets are not suitable for intravaginal administration. Such granulates are prepared
- 15 by wet granulation in a mixer granulator or in a fluidized bed granulator and contain 50% or about 64% by weight of furazidin, gelatinized corn starch or sucrose as a filler, sucrose or a mixture of acrylate/methacrylate polymers as a binder, talc and magnesium stearate and do not include any disintegrant. No filler and disintegrant are incorporated extragranularly before tableting; as a consequence there is no
- 20 extragranular phase of the tablet that would be disintegrated faster than more tightly squeezed granulate.

- It has been recently reported that furazidin can also be used in the local treatment of bacterial vaginitis. WO2018188992 discloses furazidin for vaginal use in the treatment of a bacterial vaginal infection, in particular infection caused by *Gardnerella vaginalis* and/or *Atopobium vaginae* bacteria. Semi-solid cream and cocoa butter-based globules are also disclosed and tested for local antibacterial activity. Also proposed is exemplary tablet form prepared by direct compression, comprising 69% or 44% by weight of furazidin, and further comprising lactose, silicon dioxide, and magnesium stearate.

- 30 It has been found by the present inventors that prior art vaginal tablet obtained by direct compression of the blend of furazidin with lactose, silicon dioxide and

magnesium stearate as disclosed in WO2018188992 is not suitable for vaginal administration. The tablet does not enable proper residence time and bioavailability of furazidin at the site of administration.

Therefore, prior art does not provide tablet composition designed specifically for use in a method of treatment of bacterial vaginitis by vaginal administration and complying with specific requirements for such administration as described herein below.

Still, vaginal administration in the form of a vaginal tablet is advantageous in the local treatment of bacterial vaginitis over semi-solid forms for several reasons. The tablet is more convenient for application and insertion into vaginal cavity. Tablet is also advantageous over semi-solid intravaginal globules, mainly because globules soften and are prone to leakage at the body temperature, leading to low residence time, messiness and discomfort. Another issue to consider in the development of clinical dosage forms is that formulations that involve use of a plastic applicator could lead to problems with disposal of applicators.

Tablets offer further advantages, such as portability, precise dosing, high stability, ease of storage, handling and administration and feasibility of large-scale production at a low cost compared to semi-solid systems.

The aim of the invention was to provide furazidin in the form of a vaginal tablet that is easy applicable, without the use of any applicator-type device, so as to increase patient comfort and compliance.

The aim of the invention was also to provide furazidin in the form of a vaginal tablet that includes low percentage of furazidin and despite of this enables even distribution of the active substance. The aim of the invention was also to provide furazidin in the form of a vaginal tablet having prolonged residence time in the place of its application, i.e. vaginal cavity, and therefore increase of bioavailability and reduction of required dosage frequency. This is important in the case of furazidin, a substance having very low water solubility, the more important in the case of vaginal administration when very low water amount is available at the site of administration for disintegration and dissolution.

Furthermore, to enable easy manipulation and insertion without any applicator, a vaginal tablet should have quite large dimensions. As a consequence, the percentage of furazidin in the tablet would be quite low, much lower than in tablets designed for oral administration. This leads to the problems with required content uniformity of tablets. The problem of uniformity in the case of tablets produced by direct compression should be dealt with by the use of a premix furazidin/silicon dioxide with relatively high amounts of silicon dioxide.

Therefore, there is a need for a furazidin vaginal tablet that enables even distribution, high residence time and fast disintegration in the site of administration. There is also a need for furazidin vaginal tablet of high dimensions and low furazidin content without loss of content uniformity, i.e. ensuring at the same time suitable average content and uniformity of furazidin content throughout the batch of the tablets during tableting. Furthermore, there is a need for a tablet that can be prepared in a smooth industrial process, from easy processable tableting mass.

Summary of the invention

According to the invention, there is provided a pharmaceutical composition of furazidin for vaginal administration in the form of a tablet that fulfills above mentioned criteria, as well as a process of preparation of such a composition.

According to the invention, a pharmaceutical composition of furazidin is in the form of a vaginal mucoadhesive tablet, comprising or consisting of:

a) a granulate containing furazidin, a pharmaceutically acceptable mucoadhesive polymeric binder and intragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more intragranular fillers and an intragranular disintegrant; and

b) extragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more extragranular fillers, an extragranular disintegrant and a lubricant,

and wherein the tablet comprises from 1 to 15% by weight of furazidin with respect to the tablet.

According to the invention there is also provided a process of the preparation of a pharmaceutical composition of furazidin in the form of a mucoadhesive tablet for vaginal administration, said process comprising or consisting of the following steps:

- a) granulation of a mixture of furazidin and intragranular excipients with an aqueous solution of a mucoadhesive binder to prepare a granulate;
- b) adding extragranular excipients to the granulate to prepare a blend, and
- c) compressing the blend into the tablet.

The tablet of the invention or prepared according to the process of the invention is useful in treating bacterial vaginitis by local administration, i.e. by administration into vaginal cavity.

According to the invention there is also provided a pharmaceutical composition of furazidin in the form of a mucoadhesive tablet, said tablet comprising or consisting of:

- a) a granulate containing furazidin, a pharmaceutically acceptable polymeric mucoadhesive binder, and intragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more intragranular fillers and an intragranular disintegrant; and
- b) extragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more extragranular fillers, an extragranular disintegrant, and a lubricant,

and wherein the tablet comprises from 1 to 15% by weight of furazidin with respect to the weight of the tablet,

for use in a method of treatment of vaginal infections by intravaginal administration of the said tablet.

Detailed description of the invention

The term "vaginal tablet" relates to the tablet that is destined for administration to the vaginal cavity, but otherwise is prepared from the pharmaceutically acceptable excipients that are conventionally used for the preparation of conventional oral tablets and using conventional tableting techniques known as such in the field of pharmaceutical technology. It has therefore advantage of easy manufacture using conventional tableting process.

Vaginal tablet comprises furazidin in a matrix comprising mucoadhesive polymer (i.e. polymeric binder) that is hydrophilic and thus wettable/swellable and able to form a gel in water environment.

The term “mucoadhesive” refers to the phenomenon of mucoadhesion, i.e. the state in which due to the presence of a mucoadhesive polymer (i.e. polymeric binder) the bond, such as a physical one, is formed for a period of time between vaginal mucosa and the tablet by means of interfacial forces.

The result of the mucoadhesion is the adherence of the tablet to the vaginal mucosa in the intimate contact due to wetting and swelling. Subsequently, the tablet disintegrates in the vagina and release the drug in a controlled manner by diffusion through swollen mucoadhesive polymer and progressive dissolution of the gel matrix.

The terms “granulate”, “intragranular”, “extragranular”, “excipients”, “binder”, “filler”, “disintegrant”, “lubricant” have the conventional meaning such as commonly used in the technology of oral solid forms.

By excipient it is meant any component other than the active ingredient furazidin, i.e. pharmaceutically acceptable inactive ingredient that is commonly used to prepare tablets for oral administration.

Intragranular excipients are the fraction of excipients added during the granulation process and present in the granulate obtained.

Extragranular excipients are the fraction of excipients added as a powder to the granulate after granulation process to obtained a blend and before compression or tableting process of the blend.

The mucoadhesive tablet of the invention comprises 1 to 15% by weight of furazidin.

Preferably, the tablet of the invention comprises 2 to 10%, such as 2.5 to 10% by weight of furazidin.

In one embodiment, the tablet of the invention comprises 2.5% by weight of furazidin.

In another embodiment, the tablet of the invention comprises 10% by weight of furazidin.

The tablet of the invention may comprise from 2.5 to 100 mg of furazidin per unit dosage form, i.e. tablet (furazidin dose strength). In specific embodiments, furazidin dose strength is selected from the group consisting of 5 mg, 25 mg, 50 mg and 100 mg. Preferably, tablet of the invention comprises 5 mg of furazidin per unit dosage form.

In one embodiment, the tablet of the invention comprises 2.5% by weight of furazidin and furazidin dose strength is 5 mg.

- 10 In another embodiment, the tablet of the invention comprises 10% by weight of furazidin and furazidin dose strength is selected from the group consisting of 25 mg, 50 mg and 100 mg.

In a specific embodiment, the tablet of the invention comprises 10% by weight of furazidin and furazidin dose strength is 25 mg.

- 15 In another specific embodiment, the tablet of the invention comprises 10% by weight of furazidin and furazidin dose strength is 50 mg.

In yet another specific embodiment, the tablet of the invention comprises 10% by weight of furazidin and furazidin dose strength is 100 mg.

- 20 The tablet of the invention comprises granulate a), wherein furazidin is included in a matrix comprising mucoadhesive polymeric binder.

The amount of the polymeric mucoadhesive binder in the tablet of the invention is in the range from 2 to 7%, especially 3% by weight with respect to the weight of the tablet.

- 25 The mucoadhesive polymeric binder may be selected from the group consisting of povidone, hydroxypropylmethylcelluloses (HPMC), such as HPMC-E15, hydroxypropylcelluloses (HPC), such as Klucel MXF, high molecular weight acrylic acid polymer crosslinked with divinyl glycol (polycarbophil), such as Noveon AA-1,

carboxypolymethylenes and carbomers, such as Carbopol 974 NF, and alginates, such as Protanal PH 6160.

Preferred mucoadhesive polymeric binder is povidone, especially povidone K30.

Povidone, as commonly recognized in the field of pharmaceutical technology, means
5 polyvinylpyrrolidone.

Granular and extragranular excipients comprise one or more intragranular and extragranular fillers, respectively.

The amount of one or more intragranular fillers is in the range from 20 to 80% by weight with respect to the weight of the tablet.

10 The amount of one or more extragranular fillers is in the range from 20 to 40% by weight with respect to the weight of the tablet.

The total amount (sum) of intragranular and extragranular fillers in the entire tablet is in the range from 1 to 97.5% by weight with respect to the weight of the tablet.

The intragranular and extragranular fillers may be water soluble or water insoluble.

15 The presence of water soluble and insoluble fillers and their respective weight ratio may allow to modify release properties of the tablet.

Advantageously, the intragranular excipients comprise a mixture of water soluble and water insoluble intragranular fillers.

Also advantageously, the extragranular excipients comprise a mixture of water
20 soluble and water insoluble extragranular fillers.

In a particular embodiment, the intragranular excipients comprise a mixture of water soluble and water insoluble intragranular fillers and the extragranular excipients comprise a mixture of water soluble and water insoluble extragranular fillers.

In particular, the weight ratio of water soluble filler to water insoluble filler in the tablet
25 is in the range from 3.4 : 5.6 to 7.6 : 11.9.

Water insoluble intragranular and/or extragranular filler may be selected from the group consisting of microcrystalline cellulose, calcium phosphate tribasic, dibasic

calcium phosphate, calcium sulphate and dicalcium phosphate. Preferred water insoluble filler is microcrystalline cellulose.

Water soluble intragranular and/or extragranular filler may be selected from the group consisting of lactose, sorbitol, xylitol, mannitol, amylose, dextrose and soluble
5 hydroxyalkylcelluloses. Preferred water soluble filler is lactose, especially lactose monohydrate.

Especially preferred said one or more intragranular and/or extragranular filler is a mixture of microcrystalline cellulose and lactose, especially lactose monohydrate.

Advantageously, the weight ratio of lactose monohydrate to microcrystalline cellulose
10 is 2.8 : 5.3.

In a preferred embodiment, intragranular excipients fillers and extragranular fillers are the same.

Accordingly, especially preferred said one or more intragranular fillers is a mixture of microcrystalline cellulose and lactose, especially lactose monohydrate, and said one
15 or more extragranular fillers is a mixture of microcrystalline cellulose and lactose, especially lactose monohydrate.

In a specific embodiment, said one or more intragranular fillers is a mixture of microcrystalline cellulose and lactose, especially lactose monohydrate, said one or more extragranular fillers is a mixture of microcrystalline cellulose and lactose,
20 especially lactose monohydrate, and mucoadhesive polymeric binder is povidone, especially povidone K30.

Intragranular and extragranular excipients comprise an intragranular and extragranular disintegrant, respectively.

Intragranular and extragranular disintegrant may be selected from disintegrants
25 conventionally used in tablets.

Intragranular and extragranular disintegrant may be in particular selected from the group consisting of starch sodium glycolate, corn starch pregelatinised, such as corn starch pregelatinised 1500, low-substituted hydroxypropylcellulose, cellulose microcrystalline, croscarmellose sodium and crospovidone.

Preferred intragranular and extragranular disintegrant is crospovidone, i.e. crosslinked polyvinylpyrrolidone.

Preferably, the intragranular and extragranular disintegrant is the same and is crospovidone.

- 5 The total amount of disintegrant in the tablet is in the range from 2.0 to 7.0% by weight with respect to the weight of the tablet. The weight ratio of the disintegrant in the granulate to the disintegrant in the extragranular excipients is 2:3.

Extragranular excipients comprise lubricant.

- 10 The amount of the lubricant is in the range from 0.5 to 2.0% by weight with respect to the weight of the tablet.

The lubricant may be selected from the group consisting of calcium stearate, stearic acid, palmitic acid, stearyl alcohol, polyethylene glycols (PEG), hydrogenated castor oil, hydrogenated plant oils, magnesium stearate and sodium stearyl fumarate.

- 15 Preferred lubricant is selected from the group consisting of magnesium stearate and sodium stearyl fumarate. Especially preferred is magnesium stearate.

The tablet of the invention preferably has the shape that is convenient for insertion into vagina without using any device, such as applicator. Advantageously, the tablet is almond-shaped, oval-shaped, bullet-shaped or capsule-shaped. Preferred is almond-shaped tablet pointed out at its one end.

- 20 According to the needs, if treatment of mixed vaginal infections is desired, the tablet may include further antimicrobial agent useful in the treatment of vaginal infections selected from the group consisting of antibacterial, antifungal and antiparasitic agents.

- 25 Tablet of the invention may be provided with a non-functional coating, such as colored aesthetic coating. A coating may a typical customary, ready for use coating, such as polyvinyl alcohol based coating, like Opadry.

Advantageous is the composition of the invention wherein the granulate is prepared by wet-granulation, especially by high-shear granulation.

It will be appreciated by a skilled person that wet-granulation is a granulation process, in particular using high-shear granulator, wherein a homogenous dry mixture of furazidin with intragranular excipients is prepared, a granulating liquid, such as an aqueous solution of a binder is added to the mixture, and wetted mixture is granulated with a mixer and chopper.

The object of the invention is also a process of the preparation of a pharmaceutical composition of furazidin in the form of a mucoadhesive tablet for vaginal administration, comprising or consisting of the following steps:

- a) granulation of a mixture of furazidin and pharmaceutically acceptable intragranular excipients with an aqueous solution of a polymeric mucoadhesive binder to prepare furazidin granulate;
- b) adding pharmaceutically acceptable extragranular excipients to the furazidin granulate to prepare a blend, and
- c) compressing the blend into the tablet.

Preferably, granulation is performed in a high-shear granulator.

The tablet may be also coated in a conventional coating process.

Techniques for use in the process of the invention are as such commonly known by a skilled person.

Example 1. Preparation of the tablets of the invention

Almond-shaped tablets of the furazidin strength 5 mg, 25 mg, 50 mg and 100 mg and total weight of the tablet 200 mg, 250 mg, 500 mg and 1000 mg, respectively were prepared. Composition of the tablets is presented in Table 1 below. Percentages of the granulate and extragranular phase are given in % by weight per whole tablet.

Table 1. Composition of the tablets of the invention for furazidin strength 25, 50, 100 and 5 mg

		25 mg		50 mg		100 mg		5 mg	
Component	Function	mg	% *	mg	% *	mg	% *	mg	% *
Granulate									
Furazidin	Active substance	25.00	10%	50.00	10%	100.00	10%	5.00	2.5%
Lactose, monohydrate	Filler	100.00	40%	200.00	40%	400.00	40%	95.00	43.5%
Microcrystalline cellulose,	Filler	37.50	15%	75.00	15%	150.00	15%	30.00	19%
Crospovidone (Polyplasdone XL)	Disintegrant	5.00	2%	10.00	2%	20.00	2%	4.00	2%
Povidone K30	Binder	7.50	3%	15.00	3%	30.00	3%	6.00	3%
Extragranular phase									
Lactose, monohydrate,	Filler	32.50	13%	65.00	13%	130.00	13%	26.00	13%
Microcrystalline cellulose,	Filler	32.50	13%	65.00	13%	130.00	13%	26.00	13%
Crospovidone (Polyplasdone XL)	Disintegrant	7.50	3%	15.00	3%	30.00	3%	6.00	3%
Magnesium stearate	Lubricant	2.50	1%	5.00	1%	10.00	1%	2.00	1%
Per whole tablet									
Furazidin	Active substance	25.00	10%	50.00	10%	100.00	10%	5.00	2.5%
Lactose, monohydrate	Filler	132.50	53%	265.00	53%	530.00	53%	121.00	56.5%
Microcrystalline cellulose	Filler	70.00	28%	140.00	28%	280.00	28%	56.00	22%
Crospovidone (Polyplasdone XL)	Disintegrant	12.50	5%	25.00	5%	50.00	5%	10.00	5%
Povidone K30	Binder	7.50	3%	15.00	3%	30.00	3%	6.00	3%
Magnesium stearate	Lubricant	2.50	1%	5.00	1%	10.00	1%	2.00	1%
Total mass of the tablet		250 mg		500 mg		1000 mg		200 mg	
Dimension of the tablet in mm		7.80 x 12.50		10.00 x 16.00		18.00 x 11.00 or 19.00 x 12.00 or 20.00 x 12.00		7.30 x 11.70	

* % by weight per whole tablet

Tablets have been prepared using wet-granulation technique and a high-shear granulator apparatus.

An aqueous solution of povidone K30 at 20% by weight was prepared as a granulation liquid. Furazidin was blended with the part of lactose to prepare a

furazidin premix. The furazidin premix was mixed in a mixing bowl of a high-shear granulator with microcrystalline cellulose and crospovidone to prepare a powder blend. The powder blend was fed with the granulation liquid and granulated using a high-speed impeller to obtain a wet mass. The wet mas was milled, forced through the sieve to produce wet granules, and dried. Dry granulate was mixed with extragranular components to obtain a tableting mass. Tableting mass was then compressed into tablets. The tablets were subsequently coated with a yellow Opadry polyvinyl alcohol based coating.

Example 2. Comparative tablets

Comparative tablets having composition presented in Table 2 below, which is the same as the total composition of the tablets of Example 1 for furazidin strength 50 mg were prepared without granulation.

Component	% by weight/tablet
Furazidin (50 mg)	10%
Lactose, monohydrate	53%
Microcrystalline cellulose	28%
Crospovidone (Polyplasdone XL)	5%
Povidone K30	3%
Magnesium stearate	1%

Premix of furazidin with magnesium stearate was prepared and then mixed with the rest of the components to obtain a homogenous blend. The blend was compressed using direct tableting technique, and tablets were coated with yellow polyvinyl alcohol based coating to produce comparative tablets.

Example 3. Measurement of properties of tablets

A. Mucoadhesion of the tablets

Tablets' capacity to adhere to the vaginal mucosa at the time of administration was assessed *in vitro* by measurement of the work necessary for its detachment from the mucosa (adhesion work) by means of the TA.XTplus Texture Analyser device and Exponent Connect software (both from Stable Micro Systems). The Mucoadhesion

Rig, 36 mm diameter stainless-steel cylinder probe, 5 kg loadcell, and the “Measure Distance in Compression” mode with the following program of the test were used:

Pre-Test Speed: 0.5 mm/s

Test speed: 0.1 mm/s

5 Post-Test Speed: 0.1 mm/s

Target Mode: Force

Applied Force: 0.2 N

Contact time: 30 s

Trigger Type: Force

10 Mucin disc (10% mucin solution) was used as an *in vitro* mono-component mucosa model.

Mucin disc was prepared by evenly applying 10% mucin solution on a cellulose filter and sticking it to the underside of the probe with double-sided adhesive tape.

15 Vaginal Fluid Simulant (VFS), pH=4.5, was used to mimic the environment of vaginal mucosa.

VFS was prepared as described in “A Vaginal Fluid Simulant, Derek H. Owen* and David F. Katz, Contraception 1999;59:91–95, except that pH was adjusted to 4.5 instead of 4.2.

Accordingly, the formulation for 1 L of solution given as compound and weight (g),
20 was as follows: calcium, 0.120; potassium, 0.978; sodium, 1.38; chloride, 2.13; albumin, 0.018; lactic acid, 2.00; acetic acid, 1.00; glycerol, 0.16; urea, 0.4; and glucose, 5.0. A specific “recipe” for 1 L of this simulant given as compound and weight (g), is as follows: NaCl, 3.51; KOH, 1.40; Ca(OH)₂, 0.222; bovine serum albumin, 0.018; lactic acid, 2.00; acetic acid, 1.00; glycerol, 0.16; urea, 0.4; and glucose, 5.0.
25 Once these compounds were combined, the mixture was adjusted to pH of 4.5 using HCl.

Mucoadhesion Rig was thermostated at 37°C. The samples were then prepared by fixing the whole tested tablet (n = 5 for each test) to the Mucoadhesion Rig with double-sided adhesive tape.

0.6 g of the Vaginal Fluid Simulant was applied onto the tablet fixed to the Mucoadhesion Rig. The probe with the mucin disc was moved downward at a pre-test speed 0.5 mm/s until it came into contact with the tablet, compressed at the test speed 0.1 mm/s to begin the bonding process, and predetermined compression force
5 0.2N force was applied and maintained for the dwell time 30 s.

The probe was then separated from the tablet at the speed of 0.1 mm/s until the complete detachment of the disc from the tablet. During the tests, force was measured and recorded as a function of displacement. From these adhesion curves the work of adhesion (the absolute area under the curve) and the force of detachment
10 (the maximum of the force) are determined.

Mucoadhesion (as the work of adhesion) of the tablets of the invention (Ex. 1) prepared using wet-granulation technique and comparative tablets of the same composition prepared by direct compression without granulation (Ex. 2) are 0.74 and 0.41, respectively, as presented in Table 3 below.

15 Table 3. Work of adhesion

Tablet	Work of adhesion [μ J]
Ex. 1 (wet-granulation, furazidin 50 mg)	0.74
Ex. 2 (direct compression, furazidin 50 mg)	0.41

It can be seen that mucoadhesion of the tablets containing mucoadhesive polymer prepared by wet granulation is much higher than for tablets of the same composition prepared by direct compression. High level of binding and adherence to the mucin, glycoprotein that is the main component of mucosal surfaces, enables to obtain high
20 time of residence at the site of absorption of the drug and thus improve its bioavailability. This is especially important in view of very low solubility of furazidin in water.

For comparative purposes, work of adhesion to the mucin disc in vitro was measured also for furazidin commercial tablets for oral administration. Tested products and work
25 of adhesion are presented in Table 4 below.

Table 4. Mucoadhesion of commercial tablets for oral administration

Product	uroFuragin	uroFuragin Max	Dafurag max
Furazidin strength [mg]	50	100	100
Furazidin concentration in the tablet, % w/w	50%	33.3%	24.5%
Mass of the tablet [mg]	100	300	407,5
Excipients	Corn starch, sucrose, colloidal silica, stearic acid	Lactose monohydrate, microcrystalline cellulose silicified, colloidal silica, magnesium stearate	Mannitol, lactose, colloidal silica, sodium carboxymethylcellulose, magnesium stearate, talc
Work of adhesion [μ J]	0.30	0.33	0.18

It can be seen that commercial tablets designed for oral administration are not suitable for vaginal administration because of low mucoadhesion.

B. Disintegration time

- 5 Disintegration time of the tablets was measured in accordance with European Pharmacopoeia 11.0 test for vaginal tablets 2.9.2. (Disintegration test for rectal and oral dosage forms), disintegration criterium e)).

Disintegration time of the tablets of the invention (Ex. 1) was found to be 3:30 [min:sec].

- 10 Tablets of the invention have good disintegration time of the extragranular part. This allows easy and fast spreading and distribution of the furazidin containing granulate matrix throughout the entire vaginal cavity. Therefore, release rate of furazidin from the tablets of the invention is not limited by disintegration of the extragranular phase.

Claims

Claim 1. A pharmaceutical composition of furazidin in the form of a vaginal
5 mucoadhesive tablet, said tablet comprising or consisting of:

a) a granulate containing furazidin, a pharmaceutically acceptable polymeric
mucoadhesive binder, and intragranular pharmaceutically acceptable
excipients, said excipients comprising or consisting of one or more
intragranular fillers and an intragranular disintegrant; and

10 b) extragranular pharmaceutically acceptable excipients, said excipients
comprising or consisting of one or more extragranular fillers, an extragranular
disintegrant, and a lubricant,

and wherein the tablet comprises from 1 to 15% by weight of furazidin with respect to
the weight of the tablet.

15 Claim 2. The composition of claim 1, wherein the amount of furazidin is from 2.5
to 10% by weight with respect to the weight of the tablet, especially 2.5% by weight or
10% by weight of the tablet.

Claim 3. The composition of any one of claims 1 to 2, wherein the amount of the
polymeric mucoadhesive binder is in the range from 2 to 7%, especially 3% by weight
20 with respect to the weight of the tablet.

Claim 4. The composition of claim 3, wherein the mucoadhesive binder is
povidone, especially povidone K30.

Claim 5. The composition of any one of claims 1 to 4, wherein said intragranular
and/or extragranular one or more fillers is selected from the group consisting of lactose,
25 microcrystalline cellulose and their mixtures.

Claim 6. The composition of any one of claims 1 to 5, wherein both intragranular
and extragranular one or more fillers is a mixture of lactose and microcrystalline
cellulose.

Claim 7. The composition of any one of claims 1 to 6, wherein said one or more intragranular fillers is a mixture of microcrystalline cellulose and lactose, especially lactose monohydrate, said one or more extragranular fillers is a mixture of microcrystalline cellulose and lactose, especially lactose monohydrate, and
5 mucoadhesive polymeric binder is povidone, especially povidone K30.

Claim 8. The composition of any one of claims 1 to 7, wherein the intragranular and extragranular disintegrant are selected from the group consisting of starch sodium glycolate, corn starch pregelatinised, such as corn starch pregelatinised 1500, low-substituted hydroxypropylcellulose, cellulose microcrystalline, croscarmellose sodium
10 and crospovidone.

Claim 9. The composition of claim 8, wherein the intragranular disintegrant and extragranular disintegrant are the same.

Claim 10. The composition of claim 9, wherein the intragranular disintegrant is crospovidone and extragranular disintegrant is crospovidone.

15 Claim 11. The composition of any one of claims 1 to 10, wherein the lubricant is magnesium stearate.

Claim 12. The composition of any one of claims 1 to 11, wherein a furazidin dose strength is from 2.5 to 100 mg.

Claim 13. The composition of claim 12, wherein the furazidin dose strength is selected
20 from the group consisting of 5 mg, 25 mg, 50 mg and 100 mg, preferably is 5 mg.

Claim 14. The composition of any one of the preceding claims, wherein the granulate is prepared by wet-granulation, especially by high-shear granulation.

Claim 15. A process for the preparation of a pharmaceutical composition of furazidin in the form of a mucoadhesive tablet for vaginal administration as defined in
25 any one of claims 1 to 14, comprising or consisting of the following steps:

- a) granulation of a mixture of furazidin and intragranular excipients with an aqueous solution of a polymeric mucoadhesive binder to prepare furazidin granulate;

- b) adding extragranular excipients to the furazidin granulate to prepare a blend, and
- c) compressing the blend into the tablet.

5 Claim 16. The process of claim 15, wherein the granulation is performed in a high-shear granulator.

Claim 17. A pharmaceutical composition of furazidin in the form of a mucoadhesive tablet, said tablet comprising or consisting of:

- 10 a) a granulate containing furazidin, a pharmaceutically acceptable polymeric mucoadhesive binder, and intragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more intragranular fillers and an intragranular disintegrant; and
- b) extragranular pharmaceutically acceptable excipients, said excipients comprising or consisting of one or more extragranular fillers, an extragranular disintegrant, and a lubricant,

15 and wherein the tablet comprises from 1 to 15% by weight of furazidin with respect to the weight of the tablet,

for use in a method of treatment of vaginal infections by intravaginal administration of the said tablet.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/079722

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/00 A61K9/20 A61K31/00 A61K31/4178 ADD.		
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 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) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2022/157357 A1 (ADAMED PHARMA S A [PL]) 28 July 2022 (2022-07-28)	1 - 17
Y	page 1, lines 5-6 example 1, tables 1-2, pages 29-35 -----	15, 16
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X	WO 2018/069804 A2 (PRZED PRODUKCJI FARMACEUTYCZNEJ HASCO LEK S A [PL] ET AL.) 19 April 2018 (2018-04-19)	1 - 14, 17
Y	examples 9-15, pages 18-28 claims -----	15, 16
☐ 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 "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 13 January 2025		Date of mailing of the international search report 24/01/2025
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Leitner, Nikolaus

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Information on patent family members

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