



Oifig
Na
bPaitinní

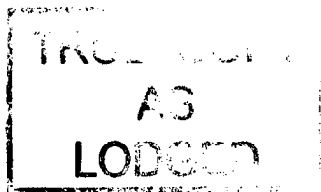
The
Patents
Office

IE 2007/0121

ABSTRACT

The present invention is directed to a process for preparing an orally administered unit dose tablet comprising bisoprolol fumarate and to an orally administered unit dose tablet comprising bisoprolol fumarate.

IE0 70 121



**"A Process for the Preparation of an Orally
Administered Unit Dose Tablet"**

FILE NO. (wob)
ABIK 9/26
ABIP 9/00

ORDER NO. 2113
JUL 10 2008

5 Field of the Invention

The present invention is directed to a process for preparing an orally administered unit dose tablet comprising bisoprolol fumarate and to an orally administered unit dose tablet comprising bisoprolol fumarate.

10

Background to the Invention

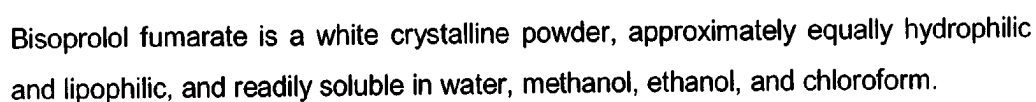
Bisoprolol fumarate is a synthetic beta₁-selective (cardioselective) adrenoceptor blocking agent. Bisoprolol fumarate is indicated for the treatment of hypertension.

15 Bisoprolol Fumarate is in a class of drugs called beta-blockers. Beta-blockers affect the heart and circulatory system (arteries and veins). Bisoprolol Fumarate is generally used for chronic, stable moderate to severe heart failure in addition to standard medicines.

20 Bisoprolol Hemifumarate has the following formula (R,S)1-[4-[[2-(1-Methylethoxy)ethoxy)methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol hemifumarate; and Bisoprolol fumarate is chemically described as (+/-)-1-(4-((2-(1-Methylethoxy)ethoxy)methyl)phenoxy)-3-((1-methylethyl)amino)-2-propanol (E)-2-butenedioate (2:1) (salt).

25

It possesses an asymmetric carbon atom in its structure and is provided as a racemic mixture. The S (-) enantiomer is responsible for most of the beta-blocking activity. Its empirical formula is (C₁₈H₃₁NO₄)₂•C₄H₄O₄ and it has a molecular weight of 766.97. Its structural formula is:



5 It will be understood in the specification that the word bisoprolol also refers to the active ingredient bisoprolol fumarate.

One of the problems associated with the large-scale manufacture of bisoprolol formulations is to produce a formulation with little product variation, in terms of uniformity of content of the tablets, hardness, disintegration and dissolution patterns, within each batch.

In addition one of the major challenges in this large-scale manufacture of a bisoprolol formulations is to formulate a homogenous blend or granule that will remain homogenous during the compression process.

Thus, there is a need to develop an industrial large-scale process for the preparation of a homogenous bisoprolol formulations which deals with these problems.

20 The present invention addresses these problems.

Statement of the Invention

According to a first aspect of the invention, there is provided a process for the
25 preparation of an orally administered unit dose tablet comprising the steps of:

- i. Providing bisoprolol fumarate in the range of 1 to 20% by weight and a binding agent in the range of 65 to 95% by weight, in a ratio of bisoprolol fumarate:binding agent of 1:10 to 1:50; wherein at least 99%

TE070121

- 5 by weight of the bisoprolol fumarate particles are less than 220 microns in diameter, at least 90% by weight of the bisoprolol fumarate particles are less than 100 microns in diameter and at least 50% by weight of the bisoprolol fumarate particles are less than 30 microns in diameter and at least 90% of the binding agent particles are less than 140 microns in diameter;
- 10 ii. Sieving the bisoprolol fumarate and binding agent and loading the sieved ingredients into a blender;
- iii. Providing a disintegrating agent in the range of 1 to 20% by weight and sieving and loading the sieved ingredients into a blender wherein at least 99% of the disintegrating agent particles are less than 110 microns in diameter;
- 15 iv. Blending the sieved ingredients to achieve uniform mixing of the ingredients for approximately 10 to 25 minutes;
- 20 v. Sieving from approximately 0.1 to 2% by weight of a lubricating agent and loading into the blender at a ratio of lubricating agent:bisoprolol fumarate of approximately 1:2 to 1:5.
- vi. Blending for approximately 5 minutes to achieve uniform mixing of the ingredients;
- 25 vii. Unloading the blended material into double polythene lined drums and transferring the blended material into a hopper;
- viii. Loading the blended material from the hopper into a tableting press compression machine;
- 30 ix. Forming unit dose tablets under direct compression to achieve unit dose tablets with friability of less than 1% after 4 minutes and a disintegration time of less than 15 minutes;
- 35 x. Discharging the tablets from the tableting press into a chute; and

IE070121

xi. Packaging the tablets obtained from step (x).

According to a second aspect of the invention, there is provided an orally
5 administered unit dose tablet comprising:

10 bisoprolol fumarate in the range of approximately 1 to 20% by weight
wherein at least 99% by weight of the bisoprolol fumarate particles are less
than 220 microns in diameter, at least 90% by weight of the bisoprolol
fumarate particles are less than 100 microns in diameter and at least 50%
by weight of the bisoprolol fumarate particles are less than 30 microns in
diameter; and/or

15 silicified microcrystalline cellulose in the range of approximately 65 to 95%
and wherein at least 90% of the silicified microcrystalline cellulose particles
are less than 140 microns in diameter and wherein the ratio of bisoprolol
fumarate:silicified microcrystalline cellulose is approximately from 1:20 to
1:50, preferably 1:30; and/or

20 sodium croscarmellose (PhEur) in the range of approximately 1 to 5%
wherein at least 98% of the sodium croscarmellose are less than 75 microns
in diameter; and/or

25 sodium starch glycolate (Type A) (PhEur) in the range of approximately 4 to
8% wherein at least 99% of the sodium starch glycolate particles are less
than 110 microns; and/or

30 magnesium stearate in the range of approximately 0.1 to 2% wherein the
magnesium particles are approximately 800 to 900 microns in diameter and
the a ratio of magnesium stearate:bisoprolol fumarate is approximately from
1:2 to 1:5, preferably 1:3.

Detailed Description of the Invention

35 In the specification the term "by weight" refers to the weight of the final composition.
The terms "bisoprolol" and "bisoprolol fumarate" are used interchangeably in the

specification.

The industrial large-scale manufacture of any drug presents the pharmaceutical manufacturer with many issues to consider.

5

In the large-scale manufacture of a tablet, it is essential that the entire batch being manufactured meets the various criteria set by regulatory legislation. In particular, each tablet within a batch must conform to the active ingredient weight specification, uniformity of content and dissolution specifications and there must be little or no product variation within a batch.

10

Product variation is usually attributed to segregation of the ingredients, in particular the active ingredient, within a batch. This is an unpredictable or random event because pockets of segregated material may end up at the tableting press at irregular intervals. If product variation is found within a batch, this could result in the batch not meeting the required standards and the subsequent wastage of an entire batch. This is expensive and time-consuming and something a pharmaceutical manufacturer will avoid.

15

The present invention is directed to solving these manufacturing problems when making an orally administered unit dose bisoprolol tablet on a large-scale.

20

The present invention also uses direct compression manufacture which is also cost effective and efficient use of manufacturing time.

25

In general terms, the process and formulation according to the invention provides a robust, simple process for producing tablets of good hardness and quality of attributes. Specifically, the process of the invention provides process for the manufacture of an orally administered unit dose bisoprolol tablet which has adequate hardness, good dissolution pattern and good uniformity when manufactured on a large-scale.

30

One of the problems the present invention overcomes is to formulate on a large-scale a homogenous blend of bisoprolol that will remain homogenous during the compression process. We have found that one of the critical points is ensure that the particle size of all ingredients are in the same order of magnitude. By doing this a

35

good flow of the homogeneous blend is maintained and segregation of the ingredients is avoided during compression.

- Furthermore, the Bisoprolol tablet of the present invention is manufactured by
- 5 direct compression i.e. blending of active with highly compressible materials lubricating with magnesium stearate and compressing instead of wet granulating the active followed by wet milling, drying, milling, blending lubrication and compression. This has advantages when manufacturing on the large-scale.
- 10 According to a preferred embodiment of the invention, there is provided a process for the preparation of an orally administered unit dose tablet comprising the steps of;
- a. Providing bisoprolol fumarate in the range of 1 to 20% by weight and silicified microcrystalline cellulose in the range of 65 to 95% by weight, in
- 15 a ratio of bisoprolol fumarate:silicified microcrystalline cellulose of 1:10 to 1:50, preferably approximately 1:30; wherein at least 99% by weight of the bisoprolol fumarate particles are less than 220 microns in diameter, at least 90% by weight of the bisoprolol fumarate particles are less than 100 microns in diameter and at least 50% by weight of the bisoprolol fumarate
- 20 particles are less than 30 microns in diameter and at least 90% of the silicified microcrystalline cellulose particles are less than 140 microns in diameter;
- b. Sieving the bisoprolol fumarate and silicified microcrystalline cellulose and
- 25 loading the sieved ingredients into a blender;
- c. Providing sodium croscarmellose (PhEur) in the range of 1 to 5% by weight and sodium starch glycolate (Type A) (PhEur) in the range of 4 to 20% by weight wherein at least 99% of the sodium starch glycolate
- 30 particles are less than 110 microns and at least 98% of the sodium croscarmellose are less than 75 microns in diameter, sieving and loading the sieved ingredients into the blender;
- d. Blending the sieved ingredients to achieve uniform mixing of the
- 35 ingredients for approximately 10 to 25 minutes;

- e. Sieving from approximately 0.1 to 2% by weight magnesium stearate and loading into the blender at a ratio of magnesium stearate:bisoprolol fumarate of approximately 1:2 to 1:5, preferably 1:3;
- 5 f. Blending for approximately 5 minutes to achieve uniform mixing of the ingredients;
- g. Unloading the blended material into double polythene lined drums and transferring the blended material into a hopper;
- 10 h. Loading the blended material from the hopper into a tableting press compression machine;
- i. Forming unit dose tablets under direct compression to achieve unit dose tablets with friability of less than 1% after 3 minutes and a disintegration time of less than 15 minutes;
- 15 j. Discharging the tablets from the tableting press into a chute; and
- 20 k. Packaging the tablets obtained from step (j).

The particle size of the active ingredient is an essential requirement for this invention and significantly improves the manufacture of a uniform tablet with the required dissolution and disintegration parameters.

25 Furthermore, the particle size of the active ingredient provides for good bioavailability of the active ingredient when administered to a patient.

Furthermore, particle size of active is important for good dissolution and bioavailability. In addition, particle size of all excipients in same range as active is important in a direct compression process in order to achieve for good homogeneity of blend which is maintained during compression.

30

According to one embodiment of the invention, a racemic mixture of bisoprolol is used.

35

According to a general embodiment of the invention, the active ingredient and the remaining excipients (including fillers, diluents, glidants and disintegrants but excluding the lubricant) are also sieved to break down agglomerates that may have formed in the excipients. Ideally, a 20# mesh is used to break down agglomerates bigger than approximately 800 to 900 microns, preferably 850 microns. Typically, a micronization sieve e.g. a Russell Sieve, is used.

According to a preferred embodiment of the invention, the lubricant is magnesium stearate and the remaining excipients include silicified microcrystalline cellulose which acts as a binding agent/diluent with good compactability and flow properties and the disintegrating agents croscarmellose sodium (cross linked sodium carboxymethyl cellulose) and sodium starch glycolate (sodium salt of carboxymethyl ether of starch).

In this embodiment, the sieved ingredients (excluding the lubricant) are mixed in a blender after sieving in a step wise fashion. This is the pre-lubrication step.

Preferably, the active ingredient, bisoprolol, is firstly sieved with the silicified microcrystalline cellulose in geometric proportion and added to the blender. Silicified microcrystalline cellulose preferably comprises approximately 98% microcrystalline cellulose and approximately 2% colloidal silicon dioxide. Ideally, a 20# mesh is used to break down lumps/agglomerations of particles which are bigger than approximately 800 to 900 microns, preferably 850 microns.

The disintegrants, croscarmellose sodium and sodium starch glycolate, are then sieved together and also added to the blender. Ideally, a 20# mesh is used to result break down agglomerates greater than approximately 800 to 900 microns.

Ideally, a double cone blender or a drum tumbler may be used. The blender is generally set at 32 revolutions per minute (rpm) for both the pre- and post-lubrication steps. Preferably, the drum blender is set at 32 ± 2 rpm and the cone blender is set at 15 ± 2 rpm. The choice of blender depends on batch size.

Blending is carried out to achieve uniformity of the active ingredient in the blend. This is generally when the homogeneity of the blend is 90 to 110% of the expected active content with a relative standard deviation (RSD) of 5% or less. Once uniformity has been tested and the desired uniformity has been reached, blending is stopped.

Ideally, blending at this step occurs for 10 to 30 minutes, preferably 20 minutes. These steps are the pre-lubrication steps.

5 The lubricant, preferably magnesium stearate, is then sieved to remove lumps/agglomeration of powders in the powder material. Again, ideally a 20# mesh is used to break down particles with an average particle size of greater than approximately 800 to 900 microns, preferably 850 microns. Typically, a Russell Sieve is used.

10 The sieved magnesium stearate is then added to the blended ingredients and blended. This is the lubrication step.

Typically, blending post-lubrication is only needed for a short time, for example three to ten minutes, preferably three to five minutes. This ensures that the magnesium
15 stearate and active ingredient are in contact for the minimum time necessary. Blending is stopped once uniformity of the ingredients in the mix has been achieved. This is generally when 90 to 110% of the active ingredient is blended with a relative standard deviation (RSD) of 5% or less.

20 Post lubrication, the blended mixture, which is also known as the tableting powder, is transferred to containers. Suitable containers include double lined polyethylene bags in High Density Polyethylene container. These drums are lined in order to ensure that contamination of the mixture is avoided and protect the product from moisture etc.

25 The tableting powder is then transferred to a hopper and loaded into the punches of a tableting press. Ideally, a rotary tablet compression machine is used.

The tableting press is set up with upper and lower punches and dies of a specific
30 diameter depending on the tablet strength being compressed.

The pressure applied in the tableting press depends on the tablet being manufactured, for example tablets may be manufactured with 1.25, 2.5, 3.75, 5, 7.5 and 10mg of active ingredient. Punches of different diameter are used depending on
35 the tablet strength and associated weight of the tablet to be compressed. Generally, compression forces applied are in the range of 1 to 5 KiloNewtons.

IE070121

Separate tooling of defined diameter is used for each strength (e.g. 10.5 FBE for 10mg tablets) to product a tablet with good hardness, disintegration and friability characteristics and with a thickness that produces an aesthetically good tablet.

5

It is desirable to obtain tablets with a friability of less than 1% after 100 revolutions or 4 minutes and a disintegration time of less than 15 minutes with appropriate hardness and thickness.

- 10 After the tablets are punched, they are collected in suitable containers for storage or packaged directly.

Preferably, the containers used according to this invention are double lined polyethylene bags in High Density Polyethylene containers. They are double lined in

- 15 order to provide the requisite contamination-free conditions.

The tablets are packaged in blister packs composed of PVC/PVDC 250/60 film and 20 um aluminium foil. This is the packaging for the market blister in cartons

- 20 All the excipients used in the unit dose tablets according to the invention are pharmaceutically acceptable excipients. Other excipients which are conventionally used in the field may also be contemplated here.

- 25 In one embodiment of the invention, silicified microcrystalline cellulose comprising microcrystalline cellulose and colloidal silicon dioxide is used as the binder/diluent. It may also function as a glidant. Colloidal silicon dioxide acts as a glidant to improve flow characteristics of the tableting powder. It may also act as a disintegrant.

- 30 The silicified microcrystalline cellulose is generally of a specific particle size wherein at least 90% of the silicified microcrystalline cellulose particles are less than approximately 140 microns in diameter.

- 35 Silicified Microcrystalline Cellulose, PROSOLV™, may be used which is a combination of 98% microcrystalline cellulose USP/NF, BP, Ph.Eur., JP and 2% colloidal silicon dioxide USP/NF, BP, Ph. Eur., JP. Other potentially suitable dispersing/disintegrant agents include colloidal silicon dioxide such as that sold under

Aerosil 200 TM and/or a non-ionic surfactant such as a polyoxyethylene derivative of a sorbitan ester marketed as Polysorbate 20TM.

5 The narrow particle size distribution for these excipients ensures a low tablet weight variation and good uniformity of the drug.

Other diluents and excipients having disintegrant, glidant and lubricant properties used in the pharmaceutical field may be used in the process of this invention.

10 The active ingredient may be present in the formulation at levels of 1.25, 2.5, 3.75, 5, 7.5 mg and 10mg.

In order to obtain the advantage of the present invention, all the ingredients should be in same particle size range to obtain a homogenous blended powder.
15 Furthermore, in addition powders are screened/sieved during production to eliminate any agglomerated particles.

A typical particle size range of a formulation according to the invention follows:

20	Bisoprolol	90% < 100 μ m
	Prosolv TM (MCC and Colloidal Silica)	90% < 138 μ m (median 50 μ m)
	Cross Carmellose Sodium	98% < 75 μ m
	Sodium Starch Glycollate	99% < 106 μ m
	Magnesium Stearate	Fine Powder

25

Ideally, the ratio of active ingredient to magnesium stearate is approximately 3:1.

In yet another embodiment of the invention, the lubricant is magnesium stearate. Other lubricants which may be used in accordance with the invention include
30 magnesium stearate, stearic acid, talcum and bentonites. It is essential in the process of the invention that the magnesium stearate is added at the latest moment possible to ensure it has the least amount of time in contact with the active ingredient. Magnesium stearate is hydrophobic and affects the solubility and dissolution profile of the active ingredient. The process of the present invention aims to minimise the
35 contact time between the blended ingredients and the magnesium stearate.

According to a preferred embodiment the orally administered unit dose tablet may comprise:

- 5 bisoprolol fumarate in the range of approximately 2 to 4% by weight wherein at least 99% by weight of the bisoprolol fumarate particles are less than 220 microns in diameter, at least 90% by weight of the bisoprolol fumarate particles are less than 100 microns in diameter and at least 50% by weight of the bisoprolol fumarate particles are less than 30 microns in diameter; and/or
- 10 silicified microcrystalline cellulose in the range of approximately 88 to 92% and wherein at least 90% of the silicified microcrystalline cellulose particles are less than 138 microns in diameter and wherein the ratio of bisoprolol fumarate:silicified microcrystalline cellulose is approximately from 1:20 to
- 15 1:50, preferably 1:30; and/or
- sodium croscarmellose (PhEur) in the range of approximately 2 to 5% wherein at least 98% of the sodium croscarmellose are less than 75 microns in diameter; and/or
- 20 sodium starch glycolate (Type A) (PhEur) in the range of approximately 5 to 7 % wherein at least 99% of the sodium starch glycolate particles are less than 110 microns; and/or
- 25 magnesium stearate in the range of approximately 0.2 to 2 % wherein the magnesium particles are approximately 800 to 900 microns in diameter and the a ratio of magnesium stearate:bisoprolol fumarate is approximately from 1:2 to 1:5, preferably 1:3.
- 30 The process of the present invention provides an advantage in terms of manufacture of a tablet on an industrial scale. The process used involves fewer manufacturing steps than conventional granulation techniques that would normally be used in the manufacture of such orally administered unit dose tablets.
- 35 According to one embodiment, the tablets made according to the present invention are packaged after production. They may be packaged in blisters made of

PVC/PVdC and hard temper aluminium foil or high density polyethylene twist-off plastic containers with white polypropylene twist-off caps. The orally administered unit dose may be in the form of tablets or capsule.

- 5 According to another embodiment of the invention, the tablets are delivered to a container and stored in contamination-free conditions prior to final packaging for the market.

For oral use, the recommended dosage is an initial dose of 1.25 mg to 10mg per day.

- 10 Preferably, the dose may be given as a single dose.

The treatment with bisoprolol fumarate is generally started with a gradual up titration according to the following general steps:

- 15 - 1.25 mg once daily for 1 week, if well tolerated increase to;
 - 2.5 mg once daily for a further week, if well tolerated increase to;
 - 3.75 mg once daily for a further week, if well tolerated increase to;
 - 5 mg once daily for the 4 following weeks, if well tolerated increase to;
 - 7.5 mg once daily for the 4 following weeks, if well tolerated increase to;
20 and
 - 10 mg once daily for the maintenance therapy.

The invention further provides an orally administered unit dose tablet as prepared by the process.

25

The invention further provides an orally administered unit dose tablet for use in treating stable chronic moderate to severe heart failure and/or hypertension.

- The invention is not limited to the embodiments described above but may be varied
30 within the scope of the claims.

The invention will now be described by reference to the following non-limiting examples and figures.

- 35 Figure 1 shows a flowchart for the manufacture of unit dose bisoprolol tablet.

As shown in Figure 1, the general method involved the steps of dispensing the ingredients (excluding the lubricant) of an appropriate particulate size and set ratio. These ingredients are then sieved in a step wise fashion and mixed in a blender. This is the pre-lubrication step.

5

A set ratio of magnesium stearate (the lubricant) to active ingredient is sieved before adding it to the blended mixture. A further mixing step is undertaken. This is the post-lubrication step.

- 10 The resultant blended ingredients are optionally transferred to a container and then transferred to a hopper.

The tableting press is filled with the blended ingredients from the hopper. The tableting press is fitted with dies and upper and lower punches of a specific diameter
15 depending on the tablet being produced.

The tableting powder is compressed to achieve tablets of set characteristics and then transferred to a container and then immediately packaged.

20 **Example 1: Manufacturing Process**

The following ingredients were used in order to make 5 different unit dose tablets. All values are given in mg.

Ingredient	10mg Tablet (mg)	7.5 mg Tablet	5mg Tablet (mg)	3.75mg Tablet (mg)	2.5m g Tablet (mg)	1.25mg Tablet (mg)	%
Bisoprolol fumarate	10.00	7.5	5.00	3.75	2.50	1.25	2.94
Silicified Microcrystalline Cellulose (PhEur) (98% Microcrystalline Cellulose & 2% Colloidal silicon dioxide)	303.24	227.43	151.62	113.72	75.81	37.91	89.19
Sodium starch glycolate	17.00	12.75	8.50	6.38	4.25	2.13	5
Cros carmellose Sodium	6.77	5.07	3.38	2.54	1.70	0.85	1.99
Magnesium Stearate PhEur	2.99	2.24	1.50	1.12	0.75	0.37	0.88
Total	340mg	255mg	170mg	127.5mg	85mg	42.5mg	100

Equipment Required:

5

Sieve with 20# screen mesh to screen agglomerated particles greater than approximately 800 to 900 microns in diameter.

Blender - Double cone blender or drum tumbler may be used.

Compression machine – Rotary Tablet Compression Machine

10

Method:

The following general method was used in the manufacture of the different unit dose tablets.

15

The ingredients (excluding the lubricant) defined in Table 1 and shown in Figure 1 were sifted through a screen on a sieve and loaded into a double cone blender. Firstly, the active ingredient and the silicified microcrystalline cellulose were sieved. Then the disintegrants, croscarmellose sodium and sodium starch glycolate were sieved. The blender was typically set to 32RPM. The double cone blender was run

20

for 20 minutes. Ideally, the double cone blender is run at 15 ± 2 rpm and the drum blender is run at 32 ± 2 rpm.

5 Magnesium stearate was then added through a screen on a sieve and placed in the double cone blender with the sieved ingredients. The blender was run for approximately 5 minutes and the blended material was unloaded into double polythene lined drums to form a tablet in a compression machine. A Rotary Tablet Compression Machine with 10.5mm FBE punches for the 10mg tablets was used in the manufacture of the tablets Typical compression forces applied are in the range
10 of 1 to 5 KiloNewtons.

The tablets were then packed in white high density polyethylene twist-off plastic containers with child-proof tamper evidence polypropylene white twist-off closure or in blisters made up of PVC/PVdC with a 20 micron hard temper aluminium foil.
15

Example 2: Stability & Dissolution Results for Bisoprolol Tablets

Stability tests of the tablets manufactured in accordance with Example 1 were carried out and these tablets were shown to be stable over a 12 month period.
20

The tablets manufactured in accordance with Example 1 are immediate release tablets which have rapid dissolution. All tablets manufactured (1.25mg/2.5mg/3.75mg/5/10mg tablets) were found to have similar dissolution profiles.
25

The results for a 5mg tablet manufactured according to the process of the present invention are shown below.

IE070121

Shelf life tests and specifications used during the stability study for 5 mg Tablets:

5

Tests	Specification												
Description	A white to off white round biconvex tablet with a break line on one side.												
Condition of Packaging	Packaging Intact												
Hardness*	Record												
Disintegration	Less than 15 minutes												
Friability*	<1% after 100 revolutions												
Average Weight:	170 mg/tablet $\pm$ 7.5% Range: 157.25 mg/tablet – 182.75 mg/tablet												
Uniformity of Mass*	No more than 2 out of 20 tablets shall deviate from the average by more than 7.5% and none deviate by more than 15%.												
Uniformity of subdivided tablets*	For half tablets not more than 2 of the individual weights should deviate from the accuracy by more than 10% and none deviate by more than 20%.												
Fischer Bisoprolol	Bisoprolol 5 mg/tablet $\pm$ 5% Range: 4.75 – 5.25 mg/tablet												
Identification*	The retention time of the major peak of the sample preparation in the assay corresponds to that of the standard solution.												
Dissolution:	Not less than 80% dissolved after 30 minutes.												
Related Substances:	<table> <tr> <td>Risoprolol Benzyl alcohol:</td><td>NMT 0.2%</td></tr> <tr> <td>Risoprolol n-propoxy derivative:</td><td>NMT 0.4%</td></tr> <tr> <td>Aldehyde compound</td><td>NMT 0.2%</td></tr> <tr> <td>Ester Compound</td><td>NMT 0.2%</td></tr> <tr> <td>Individual Unknown Impurities:</td><td>NMT 0.2%</td></tr> <tr> <td>Total impurities:</td><td>NMT 1.0%</td></tr> </table>	Risoprolol Benzyl alcohol:	NMT 0.2%	Risoprolol n-propoxy derivative:	NMT 0.4%	Aldehyde compound	NMT 0.2%	Ester Compound	NMT 0.2%	Individual Unknown Impurities:	NMT 0.2%	Total impurities:	NMT 1.0%
Risoprolol Benzyl alcohol:	NMT 0.2%												
Risoprolol n-propoxy derivative:	NMT 0.4%												
Aldehyde compound	NMT 0.2%												
Ester Compound	NMT 0.2%												
Individual Unknown Impurities:	NMT 0.2%												
Total impurities:	NMT 1.0%												
Microbial Purity: (Non-routine testing – initial, 24 and 36 months)	- Total viable aerobic count - Bacteria – not more than 10³ CFU/g - Fungi-not more than 10² CFU/g - Absence of Escherichia coli												

* Specification applies throughout shelf life, test conducted at release only.

Stability results for Bisoprolol Fumarate 5 mg Tablets stored for a period of 12 months.

Test	Specification	Initial	3 mths	6 mths	9 mths	12 mths
Appearance	A white to yellowish white round biconvex tablet with a break line on one side	Conforms	Conforms	Conforms	Conforms	Conforms
Condition of Packaging	Packaging Intact	Conforms	Conforms	Conforms	Conforms	Conforms
Hardness	Record	47N	41N	30N	40N	37N
Disintegration	<15 mins	0.42 min	0.07 min	0.18 min	0.15 min	0.2 min
Friability	<1% after 100 revolutions	0.12%	0.12%	0.17%	0.15%	0.14%
Average Weight	170 mg/tablet $\pm$ 7.5% Range: 157.25	171.45	171.64	172.6	172.04	172.39
Uniformity of mass*	No more than 2 out of 20 tablets deviate from avr by >7.5% and none deviate by >15%	Conforms	Conforms	Conforms	Conforms	Conforms
Uniformity of mass of subdivided tablets*	For half tablets not more than 20 of the individual weights deviate from avr by >7.5% and none deviate by > than 15%	84.11	86.00	NP	NP	NP
Moisture by Karl Fischer	Record	5.13%	5.19%	5.03%	5.29%	5.16%
Assay Active	Bisoprolol 5 mg/tablet $\pm$ 5% Range: 4.75 – 5.25 mg/tablet (in mg/tab.)	4.90	4.821	4.874	4.833	4.87
Identification	The retention time of the major peak of the sample preparation in assay corresponds to that of the standard solution	Conforms	Conforms	Conforms	Conforms	Conforms

	Total impurities NMT 1.0%	ND	ND	0.46%	0.056%	0.059%
Microbiology	Conforms to Ph Eur	Conforms	NP	NP	NP	NP

- To be performed at initial. ** Shall be tested for initial 24 and 36 months.
- NMT-Not more than
- ND: not detected
- NA: not applicable
- NP: Not Performed.

5

10 The stability data presented above demonstrates that the product is stable under these test conditions. Based on the available stability data a shelf-life of 3 years is justified for the product. No special storage conditions are required. No in-use storage conditions are necessary.

Claims:

1. A process for the preparation of an orally administered unit dose tablet
5 comprising the steps of:
 - i. Providing bisoprolol fumarate in the range of 1 to 20% by weight and a
10 binding agent in the range of 65 to 95% by weight, in a ratio of
bisoprolol fumarate:binding agent of 1:10 to 1:50; wherein at least 99%
by weight of the bisoprolol fumarate particles are less than 220 microns
in diameter, at least 90% by weight of the bisoprolol fumarate particles
are less than 100 microns in diameter and at least 50% by weight of the
bisoprolol fumarate particles are less than 30 microns in diameter and
15 at least 90% of the binding agent particles are less than 140 microns in
diameter;
 - ii. Sieving the bisoprolol fumarate and binding agent and loading the
sieved ingredients into a blender;
 - 20 iii. Providing a disintegrating agent in the range of 1 to 20% by weight and
sieving and loading the sieved ingredients into a blender wherein at
least 99% of the disintegrating agent particles are less than 110
microns in diameter;
 - 25 iv. Blending the sieved ingredients to achieve uniform mixing of the
ingredients for approximately 10 to 25 minutes;
 - v. Sieving from approximately 0.1 to 2% by weight of a lubricating agent
30 and loading into the blender at a ratio of lubricating agent:bisoprolol
fumarate of approximately 1:2 to 1:5.
 - vi. Blending for approximately 5 minutes to achieve uniform mixing of the
ingredients;

- vii. Unloading the blended material into double polythene lined drums and transferring the blended material into a hopper;
 - viii. Loading the blended material from the hopper into a tableting press compression machine;
 - ix. Forming unit dose tablets under direct compression to achieve unit dose tablets with friability of less than 1% after 4 minutes or 100 revolutions and a disintegration time of less than 15 minutes;
 - x. Discharging the tablets from the tableting press into a chute; and
 - xi. Packaging the tablets obtained from step (x).
2. The process according to claim 1 wherein the binding agent is silicified microcrystalline cellulose.
3. The process according to claim 2 wherein the ratio of bisoprolol fumarate:silicified microcrystalline cellulose is approximately 1:30.
4. The process according to any of claims 1 to 3 wherein the disintegrating agent is a combination of sodium croscarmellose (PhEur) in the range of 1 to 5% by weight and sodium starch glycolate (Type A) (PhEur) in the range of 4 to 20% by weight and wherein at least 99% of the sodium starch glycolate particles are less than 110 microns and at least 98% of the sodium croscarmellose are less than 75 microns in diameter.
5. The process according to any of the preceding claims wherein the lubricant is magnesium stearate.
6. The process according to claim 5 wherein the ratio of magnesium stearate:bisoprolol fumarate is approximately 1:3.
7. An orally administered unit dose tablet comprising:

IE 070121

- 22 -

5 bisoprolol fumarate in the range of approximately 1 to 20% by weight wherein at least 99% by weight of the bisoprolol fumarate particles are less than 220 microns in diameter, at least 90% by weight of the bisoprolol fumarate particles are less than 100 microns in diameter and at least 50% by weight of the bisoprolol fumarate particles are less than 30 microns in diameter; and/or

10 silicified microcrystalline cellulose in the range of approximately 65 to 95% and wherein at least 90% of the silicified microcrystalline cellulose particles are less than 140 microns in diameter and wherein the ratio of bisoprolol fumarate:silicified microcrystalline cellulose is approximately 1:30; and/or

15 sodium croscarmellose (PhEur) in the range of approximately 1 to 5% wherein at least 98% of the sodium croscarmellose are less than 75 microns in diameter; and/or

20 sodium starch glycolate (Type A) (PhEur) in the range of approximately 4 to 8% wherein at least 99% of the sodium starch glycolate particles are less than 110 microns; and/or

25 magnesium stearate in the range of approximately 0.2 to 2% wherein the magnesium particles are approximately 800 to 900 microns in diameter and the a ratio of magnesium stearate:bisoprolol fumarate is approximately 1:3.

IE070121

1/1

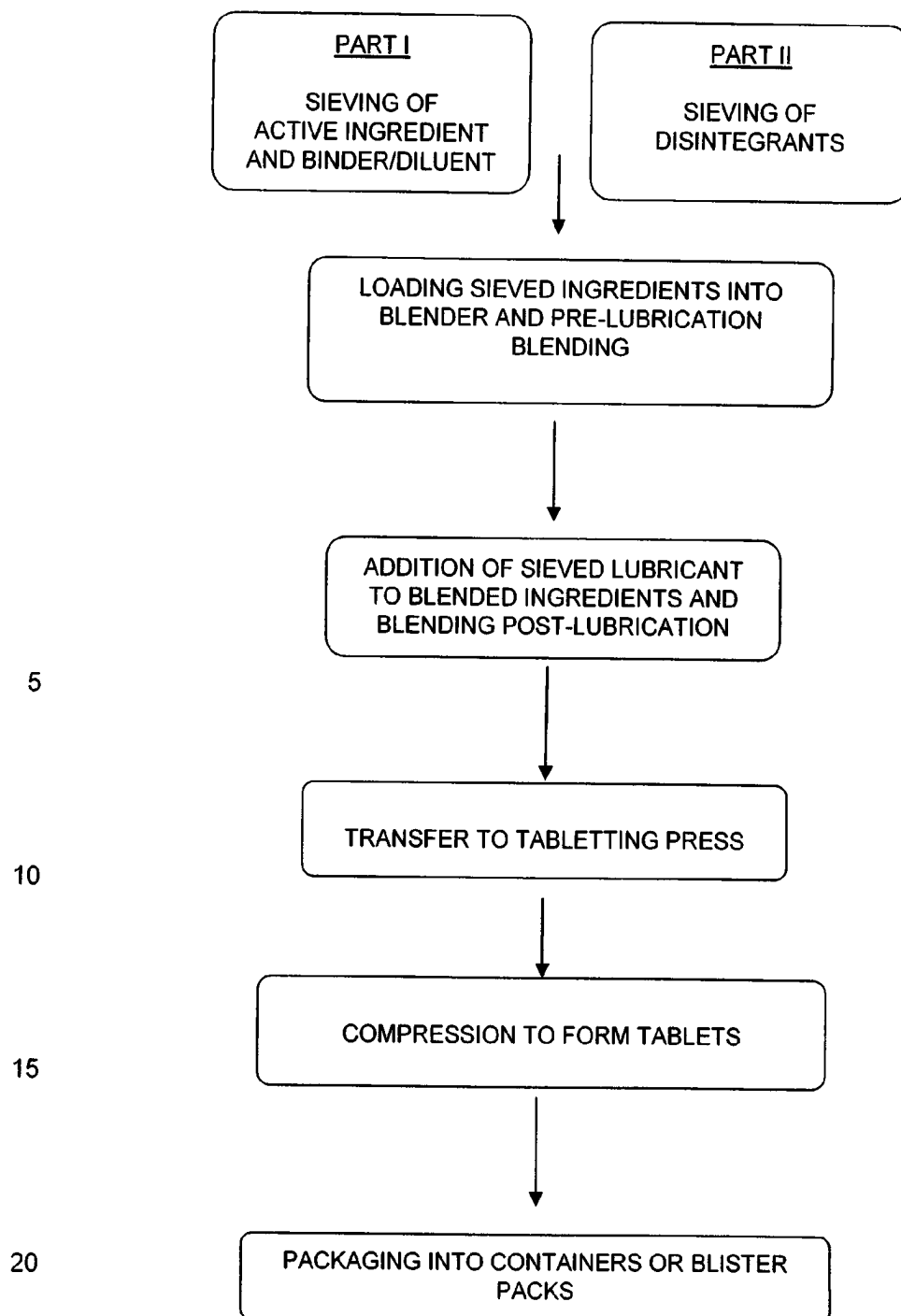


Fig. 1