The invention relates to an oral osmotic system for moderately water-soluble metoprolol salts which has improved formulation properties, and to the therapeutic use of that system in the control of disorders and conditions in which the use of beta-adrenoreceptor blocking agents is indicated.

Oral osmotic systems for the therapeutic administration of active ingredients have been known for a long time. Those systems dispense active ingredients in a controlled and delayed manner over a prolonged administration period and are described, for example, in U.S. Patent Specifications 3,845,770, 3,916,899 and 4,016,880.

An oral osmotic system for the therapeutic administration of the salt metoprolol fumarate having a semi-permeable coating made of cellulose acetate, and the in vivo release performance of that dosage form, have been described by F. Theeuwes et al. in three general articles in Br. J. Clin. Pharm., Vol. 19, 1985, on pages 69-76S, 213-218S and 219-224S.

Such dosage forms having a moderately water-soluble metoprolol salt such as metoprolol fumarate (1:1) in the core of the therapeutic system are technically disadvantageous in large-scale production, with its high requirements regarding the uniformity of the composition, and its mechanical stress: Due to the high friability of the metoprolol salt, compressed tablet cores consisting of active ingredient on its own or active ingredient with trace amounts of excipients such as poly-N-vinylpyrrolidone are too fragile to employ in conventional coating techniques, such as the Wurster air suspension technique.

Moreover, the use of relatively large amounts of excipients may be expected to interfere with the release rate

characteristics by reducing the amount of active ingredient released.

The problem underlying the present invention is to provide an industrially advantageous oral osmotic system for a moderately water-soluble, pharmaceutically acceptable metoprolol salt.

It has now been surprisingly discovered that the known and disadvantageous friability of tablet cores can be substantially eliminated by adding to the formulation composition of the core a total amount of 7.5 to 15 percent by weight poly-N-vinylpyrrolidone, based upon the total weight of the tablet core, when a moderately water-soluble, pharmaceutically acceptable metoprolol salt is used.

The oral osmotic system according to the invention comprises the following constituents:

a) an outer casing made of a semi-permeable material that is permeable to water and impermeable to the components of the core containing active ingredient;
b) a core that comprises a mixture, which is sufficiently water-soluble to produce osmotic pressure, of 7.5 to 15 percent by weight poly-N-vinylpyrrolidone, about 5 percent by weight of a glidant or lubricant customary in the preparation of solid dosage forms, and 80 to 92.5 percent by weight of a moderately water-soluble, pharmaceutically acceptable metoprolol salt; and
c) a passageway through the casing a) for transporting the constituents contained in the core into the surrounding aqueous body fluid.

The oral osmotic system according to the invention for the administration of a metoprolol salt is suitable for

use in methods for the treatment of disorders or conditions for which the use of beta$_1$-adrenoreceptor blocking agents (beta blockers) is indicated. Preferred indications are those which are known for metoprolol itself and its pharmaceutically acceptable salts, especially hypertension, angina pectoris, cardiac arrhythmias, or in the after-care of patients with myocardial infarction.

In the case of the commercial metoprolol tartrate preparation, the release behaviour of the dosage form is characterised by the immediate release of the active ingredient. There is no rate-controlled, continuous release behaviour. Where multiple dosing is required, such formulations produce large variations in the blood plasma level between high and low concentrations of the active ingredient, while reducing the effectiveness of the beta blockade. Although frequent administration of the active ingredient may prevent the blood plasma level from falling below the therapeutic level, on the whole it puts a strain on the organism. In addition, there is the danger that the active ingredient may unintentionally be taken irregularly. Different administration intervals are prescribed for that active ingredient, and they must be complied with exactly; for example, once per day for preventing hypertension, twice per day for reducing the risk of re-infarction and in indications of angina pectoris, and three times per day for preventing cardiac arrhythmias.

The oral osmotic system according to the invention permits a once daily administration for all the mentioned indications; of the unit dose of about 60 to 500 mg of metoprolol, about 50 to 90 percent of the total amount is released at the continuous release rate of about 5 to 12 percent per hour.

The subject of the present invention is described below:

The oral osmotic system according to the invention comprises a moderately water-soluble, pharmaceutically acceptable metoprolol salt and is suitable for releasing a fixed amount of active ingredient, about 50 to 500 mg of metoprolol, about 60 to 90 percent of the metoprolol salt being released at a substantially continuous rate of about 5 to 12 percent by weight, based upon the total weight of the formulation.

The pharmaceutically acceptable metoprolol salt used in the dosage form according to the invention is only moderately water-soluble and dissolves slowly in the aqueous medium after oral ingestion, as a result of fluid, in the gastrointestinal tract, passing through the semi-permeable wall of the system by diffusion, reaching the core of the system and there continuously forming an osmotically active solution of dissolved metoprolol salt. The solution enriched with dissolved metoprolol salt exhibits an osmotic pressure gradient against the aqueous fluid in the gastrointestinal tract. The active ingredient solution is released through one or more passageways in the casing of the therapeutic system which connect the core and the surrounding body fluid, so that the metoprolol salt is dispensed in a delayed and controlled manner, preferably at a constant rate (zero order). The influx rate of fluid through the semi-permeable casing is controlled by the continuous dissolution rate in the core of the system. There is used as the metoprolol salt only such a salt having moderate water-solubility, which ensures that the active ingredient is released slowly and continuously from the core of the system.

Preferably, a pharmaceutically acceptable salt of

metoprolol which is suitable for use in oral osmotic systems has a solubility of about 0.1 to 0.6 g per cm^3 at about 37°C. Suitable metoprolol salts are the lower alkanoates, especially the mono- or di-metoprolol salts of lower alkylene dicarboxylic acids, for example the fumarate or maleate mono- or di-salts of metoprolol. Especially preferred is mono-metoprolol fumarate (1:1).

The outer casing a) made of a semi-permeable material that is permeable to water and impermeable to the components of the core containing active ingredient has film- or layer-forming properties and is inert both towards the constituents of the core containing active ingredient and towards the surrounding body fluid. The material must be pharmaceutically acceptable, permeable to the surrounding body fluid and substantially impermeable to the metoprolol salt. The material is sparingly soluble in the surrounding body fluid or is soluble to such an extent that it is dissolved only towards the end of passage through the gastrointestinal tract. Suitable materials for forming the outer casing are, for example, known for the production of osmotic membranes or reverse osmosis membranes and are in some cases commercially available, for example cellulose acetate, cellulose triacetate, agar acetate, amylose triacetate, beta-glucan acetate, beta-glucan triacetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose acetate propionate, poly(vinyl methyl ether) polymers, cellulose acetate octate, cellulose acetate laurate, methyl cellulose, cellulose acetate p-toluenesulfonate, ethyl cellulose, triacetate of locust bean gum, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylated ethylene-

vinylacetate, osmotic membranes made from polymeric epoxides, alkylene oxide-alkyl glycidyl ethers, polyurethanes, polyglycolic acid, and customary polycation-polyanion membranes.

Generally, suitable membranes for fluids have a permeability of about 0.01 to 10 ml/cm^2 per hour or day at atmospheric pressure or elevated pressure against a saturated product solution at about 30°C, and at the same time are impermeable to metoprolol salts.

Especially preferred membrane materials are polyurethanes, methyl cellulose, ethyl cellulose, and cellulose acetate butyrate. Especially preferred is cellulose acetate.

The mentioned semi-permeable membrane materials are known and they, together with their properties and possible uses, are described in U.S. Patent Specification 3,916,899.

Lubricants customary for the preparation of solid dosage forms are, for example, silica, talc, and high molecular weight polyethylene glycol. Especially preferred is magnesium stearate, especially in an amount of about 1 to 5 percent, preferably about 2 to 4 percent, based upon the total core weight.

The poly-N-vinylpyrrolidone present in the core b) is water-soluble or swellable and has an average molecular weight of about 10 000 to 700 000, preferably 10 000 to 100 000. Synonymous names are polyvidone, polyvinylpyrrolidone, povidone, PVP, KOLLIDON (BASF), or PLASDON (GAF Corp.). The amount of poly-N-vinylpyrrolidone present in the core of the oral osmotic system is 7.5 to 15 percent by weight, based upon the total weight of the

core b).

Preferably, the amount of poly-N-vinylpyrrolidone present in the core is 8.5 to 13.0 percent. Pharmaceutical grade poly-N-vinylpyrrolidone is used. Reference is made to the purity specifications, for example according to U.S. Pharmacopoeia (USP), British Pharmacopoeia (BP) or Deutsches Arzneibuch 7. Especially preferred is poly-N-vinylpyrrolidone having a K value of 30, which corresponds to an average molecular weight of about 40 000.

The amount of metoprolol salt present in the core b) can vary and corresponds to the maximum and minimum permissible dosages for the active ingredient metoprolol. 50 to 500 mg of metoprolol may be present in the therapeutic system, preferably 60 to 200 mg of active ingredient.

The core b) is preferably in the form of a tablet which is coated with the membrane material of the casing a). The core may be prepared, for example, by compressing the moderately water-soluble metoprolol salt with the poly-N-vinylpyrrolidone directly, while dry, or in the form of granules. The latter are prepared, for example, by mixing and pre-drying an aqueous ethanolic suspension of the components and comminuting and drying the residue, or by dissolving or suspending the metoprolol salt in an aqueous ethanolic solution of poly-N-vinylpyrrolidone, pre-drying, comminuting, removing the residual solvent, milling the granules to a uniform particle size, and compressing the granules in the presence of a lubricant, such as magnesium stearate, to form tablet cores.

By using poly-N-vinylpyrrolidone as an excipient in the given amount of 7.5 to 15 percent, preferably 8.5 to 13 percent, it is possible to prepare tablet cores of suitable hardness, whose degree of hardness is about

8-25 SCU (Strong Cobb Units, Strong Cobb hardness tester, p. 1608 Remington's Pharmaceutical Sciences, March 1985), especially 8-20 SCU, and whose breaking strength, measured as the percentage of broken tablet cores, is not greater than 2.5 %, especially not greater than 1 %.

The outer casing a) may be applied to the core containing the active ingredient by pouring, moulding, spraying, or by immersing the capsule in the material forming the semi-permeable casing. Another method which may be used to apply the casing is the air suspension procedure. That procedure consists in suspending and agitating the compositions (capsules or capsule cores) in a stream of air and an agent forming the casing until the casing surrounds and covers the core. The air suspension procedure is described in U.S. Patent Specification 2,799,241 and in J. Am. Pharm. Assoc., Vol. 48, p. 451-459, 1979, and in Vol. 49, p. 82-84, 1980. Other preferred standard procedures are, for example, the spray pan procedure, which is described in Remington's Pharmaceutical Sciences, 14th Edition, on pages 1686-1687. When cellulose acetate is used as the membrane-forming semi-permeable material, the casing a) accounts for about 4-30 percent (by weight), preferably 10-20 percent, of the total weight of the formulation.

The expression "passageway through the casing a) for transporting the constituents contained in the core into the surrounding aqueous body fluid" includes devices and methods which are suitable for releasing the active ingredient formulation from the core of the therapeutic system. The expression covers passages, openings, drill holes, holes and the like through the casing a) acting as the semi-permeable membrane, which connect the surface of the casing and the core. The passageway may be produced by mechanical drilling or laser drilling, or by the

decomposition of a degradable constituent, for example a gelatin plug, to form a passageway in the casing of the therapeutic system. In one embodiment, the passageway may form as a reaction to the hydrostatic pressure which acts on the therapeutic system. In another embodiment, two or more passageways may be produced at any desired point in the system. The passageway may also be formed as a result of mechanical breaking open of the layers during use of the system. The passageway has a minimum diameter, which is dependent upon the particle size of the active ingredient crystals. The diameter of the passageway must be greater than the average length of the active ingredient crystals. The maximum diameter is likewise fixed approximately. It may be only so large that the penetration by convection of aqueous body fluid into the therapeutic system is avoided. A precise description of the production of the passageway and the maximum and minimum dimensions thereof is given in U.S. Patent Specifications 3,485,770 and 3,916,899 and the associated drawings. In a preferred embodiment, the size of the opening is about 0.1 to 0.8 mm.

The therapeutic system according to the invention may be of various shapes, for example, round, oval, oblong, cylindrical, etc., and of various sizes depending upon the amount it contains. Moreover, the therapeutic system may be transparent, colourless or coloured and, where appropriate, may be labelled in order to give the product an individual appearance or to make it instantly recognisable.

The passageway in the semi-permeable casing may then be produced by drilling mechanically or using a laser. The following Examples illustrate the invention.

Example 1:

To 95.37 parts by weight of metoprolol fumarate (1:1 salt) there are added 8.10 parts by weight of povidone (PLASDON K-30 GAF), and the mixture is milled to a powder and granulated with an ethanol/water mixture (70/30). The granulation mixture is then dried and sieved, and 1.53 parts by weight of magnesium stearate are mixed therewith. The granulate mixture is then compressed into tablet cores which, with a total weight of 105 mg, comprise 7.7 % by weight povidone and 1.5 % by weight magnesium stearate, the remainder being made up of the active ingredient component in the form of the metoprolol salt. The tablet cores exhibit the following mechanical characteristics:

Hardness (Strong Cobb Unit, SCU): 9-11
Breaking strength (percentage of tablet cores broken): 0.2
Disintegration time: 9 minutes.

Example 2:

Comparison of the breaking strength of tablet cores having a lower content of poly-N-vinylpyrrolidone. Otherwise, preparation analogous to Example 1.

	Constituents in parts by weight	% by weight
Metoprolol fumarate (1:1)	95.37	93.5
Povidone USP	5.10	5
Magnesium stearate NF	1.53	1.5

Hardness : 7-9
Breaking strength : 7.2 (coated tablet cores)
Disintegration time : 8 minutes

Examples 3-6:

Analogously to the procedure of Example 1, the following tablet cores are prepared:

Example	3	4	5	6
Metoprolol fumarate (1:1)	95.37	95.37	95.37	95.37
Povidone, USP	10.10	13.10	8.10	11.10
Magnesium stearate NF	1.53	1.53	2.53	2.53
% povidone	9.4	12.0	7.6	10.2
% magnesium stearate	1.4	1.4	2.4	2.3
Hardness (SCU)	14-15	11-18	9-11	8-11
Breaking strength	0.3	0.2	0.2	0.2
Disintegration time (min.)	7	8	18	15

Example 7:

According to the procedure described in Example 1, tablet cores are prepared which contain per core 95 mg of metoprolol fumarate, 2.9 mg of magnesium stearate NF and 11.10 mg of povidone USP (PLASDON K-30) and which have a degree of hardness of 8-11 (SCU), a breaking strength of 0.2 % and a disintegration time of 15 minutes. The tablet cores are coated by the Wurster air suspension procedure with a solution of cellulose acetate in a methanol/methylene chloride mixture, so that each tablet is coated with 16 mg of cellulose acetate. An opening having a diameter of about 0.5 mm is drilled into that layer.

Example 8:

Coated tablet cores are prepared and drilled analogously to Example 7. The therapeutic system so obtainable has the following composition per tablet in the core: metoprolol fumarate: 190.74 mg; povidone USP (PLASDON

K-30): 22.20 mg; and magnesium stearate: 5.06 mg. The core has the following mechanical characteristics: degree of hardness (SCU): 11-16; breaking strength: 0.2 %; disintegration time: 27 minutes. The core is coated with a coating of cellulose acetate (27 mg), in which an opening having a diameter of 0.5 mm is provided. Analogously to the methods described in U.S. Pharmacopoeia p. 1243-1244 for the measurement of dissolution processes of solid dosage forms, the release characteristics of a therapeutic system at 37°C in simulated gastric fluid (without enzymes) at a stirring speed of 100 rpm are studied, and the following values are determined:

Time [h]	Average release rate [mg/h]	Average cumulative release [%]
0 - 2	17.8 ± 2.7	18.7
2 - 4	21.4 ± 1.6	41.2
4 - 6	19.0 ± 0.9	61.2
6 - 8	17.0 ± 1.6	79.0
8 - 10	8.3 ± 1.4	87.7
10 - 12	4.5 ± 0.7	92.5

Patent claims (for all designated Contracting States except Spain and Greece):

1. An oral osmotic system for the administration of metoprolol, comprising:
a) an outer casing made of a semi-permeable material that is permeable to water and impermeable to the components of the core containing active ingredient;
b) a core that comprises a mixture, which is sufficiently water-soluble to produce osmotic pressure, of 7.5 to 15 percent by weight poly-N-vinylpyrrolidone, about 5 percent by weight of a glidant or lubricant customary in the preparation of solid dosage forms, and 80 to 92.5 percent by weight of a moderately water-soluble, pharmaceutically acceptable metoprolol salt; and
c) a passageway through the casing a) for transporting the constituents contained in the core into the surrounding aqueous body fluid.

2. An oral osmotic system according to claim 1, wherein the core b) comprises 8.5-13 % poly-N-vinylpyrrolidone.

3. An oral osmotic system according to claim 1, wherein the core b) comprises 8.5-13 % poly-N-vinylpyrrolidone having an average molecular weight of about 40 000.

4. An oral osmotic system according to claim 1, wherein the core b) comprises the fumarate salt of metoprolol (1:1) as the moderately water-soluble, pharmaceutically acceptable metoprolol salt.

5. An oral osmotic system according to claim 1, wherein the casing a) consists of cellulose acetate.

6. An oral osmotic system according to claim 1, wherein the amount of metoprolol salt contained in the casing b)

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corresponds to 60 to 200 mg of free metoprolol.

7. An oral osmotic system according to claim 1, wherein the glidant or lubricant is magnesium stearate.

8. An oral osmotic system according to claim 1 for use in a therapeutic method wherein the use of beta-adreno-receptor blocking agents is indicated.

9. A process for the preparation of an oral osmotic system according to claim 1, which comprises producing the core b) by means of customary tabletting processes by direct compressing or granulating, covering the core with the outer casing a) and forming the passageway c) in the casing.

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