Oral osmotic delivery systems are known. Those therapeutic systems in the form of coated tablets dispense the active ingredient in a controlled and continuous manner over a prolonged period of time and are described, for example, in U.S. Patent Specifications 3,845,770, 3,916,899 and 4,016,880.

Such systems in the form of tablets are characterised by an outer semi-permeable wall membrane which is permeable to body fluid in the gastrointestinal tract, by a core containing active ingredient, which core may contain pharmaceutical excipients, such as binders, osmotically active driving solutes and other tabletting excipients, and by at least one passageway through the outer semi-permeable membrane through which the active ingredient is released and which produces a flow of material between the core containing the active ingredient and the external environment.

After administration, the therapeutic system in the gastrointestinal tract imbibes body fluid through the semi-permeable outer membrane by the action of diffusion. The body fluid then dissolves the active ingredient and/or the osmotic driving solute to form a solution or at least a suspension which exhibits an osmotic pressure or a pressure gradient against the outer rigid semi-permeable membrane. As the outer membrane is rigid and is permeable only to water and not to the constituents of the osmotically active solution or suspension, the osmotic pressure can be equalised only by release from the inside of the system, so that the osmotically active constituents of the resulting solution or suspension, containing the active ingredient, leave the therapeutic system through the free passageway in the outer membrane. Since, following ingestion of the therapeutic system, equilibrium processes occur in contact with body fluid,

the active ingredient is released in a controlled, continuous and delayed manner. Materials suitable for the preparation of the outer semi-permeable membrane, and the functioning of and preparation parameters for the oral osmotic systems, are described in U.S. Patent Specification 3,916,899.

Many solid active ingredients and osmotic driving solutes contained in the core of such systems possess unsatisfactory binding capabilities to the film-like material forming the outer semi-permeable wall membrane. Even when such a core is coated uniformly with the film-like coating materials, systems having unsatisfactory binding capabilities between the inner core and the outer semi-permeable wall membrane are obtained. The risk that the outer membrane may peel away from the core is especially great. That problem is particularly serious with the frequently used coating methods, when shaped tablet cores are sprayed with solutions containing the coating composition for the outer semi-permeable wall membrane, for example when the conventional air suspension techniques, such as the Wurster air suspension technique, are used. In such processes, the core tablet may also pick up a static charge, further reducing uniform adhesion between the core and the membrane.

Even when relatively large amounts of conventional polymeric binders, such as poly-N-vinylpyrrolidone, poly-C_2-C_3alkylene glycols or hydroxyalkylcellulose ethers, or mixtures thereof, are used and are uniformly distributed in the material forming the tablet core, poor adhesion between the core itself and the outer wall membrane is observed, which manifests itself in peeling of the membrane material on contact with water or body fluid.

The use of relatively large amounts of polymeric binders

is disadvantageous where the core of the therapeutic system must also accommodate relatively large amounts of active ingredient for a unit dose. It is then necessary to prepare a bulky system, administration of which is difficult. In addition, relatively large amounts of polymeric binders may interfere with the desired controlled and continuous release profile of the active ingredient by excessively retarding the release of the active ingredient below the therapeutic level, or may clog one or more passageways and thus cause the system to rupture.

The problem underlying the present invention is to prepare an improved oral osmotic delivery system comprising the active ingredient metoprolol. The delivery system is to have improved adhesion of the outer semi-permeable wall membrane to the shaped inner tablet core and is to eliminate the disadvantages of the known oral osmotic systems, such as peeling of the outer layer and rupturing under the action of body fluid.

That problem is solved by the present invention, which relates to an oral osmotic delivery system that comprises the active ingredient metoprolol and has improved stability properties.

Surprisingly, it has been found that a stable oral osmotic system having improved adhesion of the outer membrane can be prepared if the core containing the active ingredient is additionally evenly coated with a thin, discrete and water-soluble inner film layer.

The core having the inner coating can be coated with the material for the semi-permeable outer membrane, which thus remains firmly bonded to the inner core.

The delivery system according to the invention is

suitable for the controlled and continuous administration of metoprolol over a prolonged period of time and releases into the gastrointestinal tract, for example, 50 to 90 % of the amount of active ingredient it contains at a release rate of 5 to 12 % per hour.

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

a) a shaped tablet core comprising an osmotically active composition comprising a pharmaceutically acceptable metoprolol salt in combination with a pharmaceutically acceptable binder customary in tabletting processes and, optionally, an osmotically active driving agent and/or other pharmaceutical excipients;

b) a uniform, discrete inner layer comprising approximately from 0.3 % to 10 % (by weight) water-soluble coating composition, based on the weight of the tablet core a);

c) a discrete outer layer having membrane properties which is substantially impermeable to the active ingredient metoprolol and is permeable to body fluid in the gastrointestinal tract, and which is firmly bonded to the layer b) and coats it evenly; and

d) a passageway through the two layers b) and c) which produces a flow of material between the core a) and the external environment and releases the active ingredient metoprolol into the gastrointestinal tract.

The shaped tablet core a) comprises about 5 to 20 % by weight, preferably 8 to 15 % by weight, of binders customarily used when the conventional tabletting processes are employed, about 0 to 5 % by weight,

preferably 1 to 5 % by weight, especially 2 to 4 % by weight, of a glidant or lubricant customary in tabletting processes, about 0 to 75 % by weight, preferably 0 to 45 % by weight, especially 0 to 20 % by weight, of an osmotically active driving agent, as well as a moderately water-soluble, pharmaceutically acceptable metoprolol salt at the selected dose. The percentages indicated are based on the weight of the core a).

A moderately water-soluble, pharmaceutically acceptable salt of metoprolol is preferably metoprolol fumarate. When body fluid from the gastrointestinal tract has passed through the semi-permeable membrane c) and the water-soluble film layer b) into the core a), that salt dissolves in the aqueous phase to form, on account of its moderate water-solubility, optionally together with the osmotically active driving agent, a solution which exhibits a continuously increasing osmotic pressure against the semi-permeable membrane c). Since the semi-permeable membrane c) is rigid, the osmotic pressure building up on the semi-permeable membrane c) against the surrounding body fluid is equalised by the release of fluid containing active ingredient and the soluble constituents of the core through the passageway d) between the layers b) and c), permitting a flow of material between the core a) and the external environment. The osmotic pressure on the outer layer c) is in addition intensified or augmented by the swelling pressure of the binder present in the core a). Since it is a question of equilibrium processes due to diffusion and osmosis and their equalisation, the active ingredient is released in a continuous and controlled manner, preferably at a constant rate. The metoprolol salt, especially the fumarate salt, preferably possesses limited or only moderate solubility in aqueous body fluid, so that the release of the active ingredient can

take place in a delayed and continuous manner at a constant rate of dissolution in the body fluid imbibed by the system.

Preferably, the moderately water-soluble metoprolol salt exhibits a solubility in water of about 0.1 to 0.6 g/cm^3 at 37°C. Suitable pharmaceutically acceptable moderately water-soluble salts are, for example, lower alkanoates of mono- and di-carboxylic acids, for example the fumarate, maleate and acetate salt. The fumarate salt is especially preferred for the reasons given above.

Suitable lubricants customary in tabletting processes are, for example, silica gel, starch, talc, magnesium stearate, stearic acid, and polyethylene glycols having a high molecular weight, preferably above 1000. Magnesium stearate is preferred.

The osmotically active driving agent is preferably a soluble compound, especially a carbohydrate such as glucose, saccharose, dextrose, maltose, mannitol or sorbitol, or is, for example, a water-soluble ionic salt which is compatible with the other constituents of the formulation, for example sodium or potassium chloride, or urea. Generally there may be used dissociable compounds and salts having physiological suitability.

The binder customary for tabletting processes may be selected from the known excipients mentioned in pharmacopoeias for those purposes. Especially preferred is poly-N-vinylpyrrolidone having an average molecular weight of about 10 000 to 600 000. Povidone (U.S. Pharmacopoeia) is preferred, which is commercially available under the name PLASDONE (trade mark of GAF). That specific binder is used in an amount of about 5 to 20 % by weight, preferably 8.5 to 15 % by weight and especially prefer-

ably 8.5 to 13 % by weight, based on the weight of the core.

Poly-N-vinylpyrrolidone is especially suitable as binder on account of the reduction in abrasion of the metoprolol salt in the tabletting process.

The tablet core a) is coated with a uniform, discrete inner layer of about 0.3 to 10 % by weight, preferably 0.5 to 2 %, water-soluble coating composition, based on the weight of the tablet core a). Any pharmaceutically acceptable, water-soluble coating composition having film-forming properties is suitable for the preparation of that inner layer b). Examples of suitable coating compositions are hydroxypropylmethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, polyethylene glycol and polyoxypropylene/polyoxyethylene copolymers. The polyethylene glycol which may be used preferably has an average molecular weight of about 400 to 8000. The cellulose ethers which may be used have a viscosity grade of about 3 to 4000 cps. The mentioned coating compositions having film-forming properties may also be used in the form of mixtures, preferably containing about 50 % hydroxypropylmethylcellulose. Especially preferred is a mixture of hydroxypropylmethylcellulose in combination with lesser amounts of polyethylene glycol and/or polyvinylpyrrolidone. The inner layer of water-soluble film material may also comprise up to about 10 % of an anti-tacking agent, especially talc or titanium dioxide, based on the total weight of the inner layer. The anti-tacking agent customarily has an average particle size of less than about 25 microns.

The outer casing c) made of a semi-permeable material that is permeable to body fluid 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, methylcellulose, cellulose acetate p-toluenesulfonate, ethylcellulose, triacetate of locust bean gum, cellulose acetate with acetylated hydroxyethylcellulose, 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, methylcellulose, ethylcellulose, 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.

The amount of metoprolol salt present in the core a) can vary and corresponds to the maximum and minimum permissible dosages for the active ingredient metoprolol. About 25 to 500 mg may be present in the unit formulation, based on the base. Preferably, the core comprises 30 to 400 mg, especially 100 to 400 mg or 200 to 400 mg, and most especially 250 to 400 mg, of metoprolol in the form of a pharmaceutically acceptable salt.

The core a) is preferably in the form of a tablet which is coated with the discrete inner layer b) of water-soluble film material and with the membrane material of the casing c). 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 about 7.5 to 15 %, preferably 8.5 to 13 %, 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 inner layer b) may be applied to the core a) containing the active ingredient by pouring, moulding, spraying, or by immersing the core in a solution of the water-soluble coating composition, for example hydroxypropylmethylcellulose. The material forming the semi-permeable casing c) can in turn be applied to that coated core by pouring, moulding, spraying or immersion. Another method which may be used to apply the two layers is the air suspension procedure. That procedure consists in suspending and agitating the compositions (tablets or tablet cores) in a stream of air and a composition forming the layer in question until the layers surround and cover the core in succession. 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 % (by weight), preferably 10-20 %, 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 3,845,770 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 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.

Where metoprolol tartrate is used in conventional formulations such as tablets, 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 50 to 500 mg of metoprolol, about 50 to 90 % of the total amount is released at the continuous release rate of about 5 to 12 % per hour.

The present invention relates also to a human-therapeutic method of treating disorders and/or conditions for which the use of beta$_1$-adrenoreceptor blocking agents (beta blockers) is indicated, which method comprises administering orally to the patient the above osmotic system comprising an effective unit dose of the active ingredient.

Example 1: 3800 g of metoprolol fumarate and 190 g of hydroxypropylmethylcellulose are passed through sieves having mesh sizes of 0.55 mm and 0.99 mm, respectively (30 mesh and 16 mesh, respectively (U.S. Pharmacopoeia)). The screened materials are then blended together, and the blend is granulated with a 10 % (w/v) solution of polyvinylpyrrolidone in a 70:30 mixture of ethyl alcohol and water. The granules are then dried for 16 hours at 40°C and the dried granules are milled and blended with 120 g of magnesium stearate and finally compressed into cores.

56.0 g of hydroxypropylmethylcellulose are dissolved in 750 ml of a methanol/methylene chloride mixture and the solution is used to coat the compressed cores uniformly using the air suspension procedure. 24 g of hydroxypropylmethylcellulose, 24 g of polyethylene glycol and 252 g of cellulose acetate are dissolved in 5000 ml of a methanol/methylene chloride mixture and the solution is used to coat the hydroxypropylmethylcellulose-coated cores uniformly by an air suspension procedure. The coated tablets are then drilled to produce a bore of

about 0.34 mm diameter, which passes through both outer layers.

Example 2: Analogously to the procedure of Example 1, the following oral osmotic systems are prepared:

Active ingredient	[g]	Binder	[g]	Granulator	[g]	Subcoat	[g]
Metoprolol fumarate	3800						
Metoprolol tartrate	4800						
		HPC	190				
				HPMC	190		
		HPMC	380				
				HPC	190		
		HEC	190				
		PVP	400			HPMC	30
						HPMC PVP	30 28

HPC: hydroxypropylcellulose
HEC: hydroxyethylcellulose
PVP: polyvinylpyrrolidone
HPMC: hydroxypropylmethylcellulose

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

1. An oral osmotic system for the controlled and continuous administration of metoprolol over a prolonged period of time, comprising the following constituents:

a) a shaped tablet core comprising an osmotically active composition comprising a pharmaceutically acceptable metoprolol salt in combination with a pharmaceutically acceptable binder customary in tabletting processes and, optionally, an osmotically active driving agent and/or other pharmaceutical excipients;

b) a uniform, discrete inner layer comprising approximately from 0.3 % to 10 % (by weight) water-soluble coating composition, based on the weight of the tablet core a);

c) a discrete outer layer having membrane properties which is substantially impermeable to the active ingredient metoprolol and is permeable to body fluid in the gastrointestinal tract, and which is firmly bonded to the layer b) and coats it evenly; and

d) a passageway through the two layers b) and c) which produces a flow of material between the core a) and the external environment and releases the active ingredient metoprolol into the gastrointestinal tract.

2. An oral osmotic system according to claim 1, wherein the uniform discrete inner layer consists of hydroxypropylmethylcellulose or polyvinylpyrrolidone or mixtures thereof.

3. An oral osmotic system according to claim 1, wherein

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the uniform discrete inner layer consists of hydroxypropylmethylcellulose, polyvinylpyrrolidone or mixtures comprising up to 50 % polyethylene glycol.

4. A process for the preparation of an oral osmotic system according to claim 1, which comprises preparing the tablet core a) by compressing granules, providing the tablet core a) with the water-soluble coating composition of layer b), applying thereto the discrete outer layer c) having membrane properties, and forming the passageway d) through the layers b) and c).