

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 March 2006 (23.03.2006)

PCT

(10) International Publication Number
WO 2006/030402 A2

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 31/495* (2006.01)

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(21) International Application Number:
PCT/IB2005/053076

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:
19 September 2005 (19.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1763/Del/2004 17 September 2004 (17.09.2004) IN

(71) Applicant (*for all designated States except US*): **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, New Delhi, Delhi 110019 (IN).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **VERMA, Rajan, Kumar** [IN/IN]; House Number 1366-A Gali Sunaran, Najatgarh, New Delhi, Delhi 110043 (IN). **VISWANATHAN, Narayanan Badri** [IN/IN]; Plot No. 25, 2nd Main Road Kannan Nagar, Madipakkam, Chennai 500091 (IN). **RAGHUVANSHI, Rajeev, Singh** [IN/IN]; 605, Ivory Towers South City - I, Gurgaon, Haryana 122001 (IN). **RAMPAL, Ashok, Kumar** [IN/IN]; 14, Sewa Nagar, Ram Tirath Road, Amritsar, Punjab 143001 (IN).

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DUAL COMPARTMENT OSMOTIC DELIVERY DEVICE

(57) Abstract: The present invention relates to a dual compartment osmotic delivery device and processes for preparation thereof.



WO 2006/030402 A2

Description

DUAL COMPARTMENT OSMOTIC DELIVERY DEVICE

[1] Field of the Invention

[2] The present invention relates to a dual compartment osmotic delivery devices and processes for their preparation.

[3] Background of the Invention

[4] Doxazosin, 1-(4-amino-6, 7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1, 4-benzodioxin-2-yl)-carbonyl]-piperazine monomethanesulfonate and its pharmaceutically acceptable acid addition salts are described in U.S. Patent No. 4,188,390. Doxazosin is a quinazoline derivative that acts through selective inhibition of alpha-1 adrenoceptors and is indicated for treating hypertension, either alone or in combination with other antihypertensive agents, and for the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia. Doxazosin is well absorbed after oral administration with bioavailability of 65% and a mean plasma half-life of about eleven hours.

[5] In the treatment of hypertension and symptoms of benign prostatic hyperplasia (BPH), doxazosin therapy is initiated at a dosage of 1 mg standard immediate release dosage form per day and the dose is doubled every seven to fourteen days to a maximum recommended dose of 16 mg per day for hypertension and 8 mg per day for benign prostatic hyperplasia (BPH) till the blood pressure or urinary flow rate or BPH symptoms are controlled. This regimen can require up to three to four titration steps to achieve therapeutically effective doses in a manner likely to avoid first dose side effects. This can be achieved by developing a formulation that gradually releases doxazosin resulting in a prolonged Tmax and reduced peak to trough blood level fluctuations of doxazosin as compared to the standard immediate release dosage form commercially available.

[6] Osmotic delivery devices utilize osmotic pressure as the driving force for the delivery of the drug. In its simplest design it includes an osmotic core that includes a drug with or without an osmotic agent. The core is coated with a semipermeable membrane, and a delivery orifice is constructed with a mechanical or laser drill. When the device comes in contact with water, the water is imbibed through the semipermeable membrane and because of the resultant osmotic pressure of the core the drug is released from the orifice at a controlled rate as a saturated solution. One of the limitations of such a device is that it can be used for only highly water soluble drugs.

[7] A number of modifications of this device are available today including the 'push-pull' or 'dual compartment' osmotic device, which is a bilayer tablet that is suitable for the delivery of active ingredients with varying solubility in water. The bilayered tablet

includes a drug layer and a push layer which is surrounded by a semipermeable membrane having an orifice. The drug layer includes a gelling agent and a drug. The gelling agent may include polymers capable of forming a gel when in contact with an aqueous medium. The push layer includes an osmopolymer and osmotic agent. The osmopolymers are polymer(s) which are capable of swelling when in contact with aqueous medium and create an osmotic pressure gradient across the semipermeable membrane. The choice of the polymers may vary depending on the molecular weight. The polymers in the drug layer generally have a molecular weight lower than the polymers used in the push layer.

- [8] U.S. Patent Nos. 4,612,008; 4,765,989; and 4,837,111 disclose various dual compartment osmotic devices. The devices exemplified use polyethylene oxide in the push layer having molecular weight of about 5,000,000 to about 7,500,000.
- [9] U.S. Patent Nos. 4,946,687 and 5,030,456 disclose dual compartment osmotic devices using polyethylene oxide in the push layer having a molecular weight of about 5,000,000 to about 7,800,000.
- [10] The osmotic system of the present invention includes a semipermeable wall that surrounds a compartment containing an active ingredient. The wall is permeable to the passage of an external fluid but substantially impermeable to the passage of active ingredients. There is at least one passageway through the wall for delivering active ingredient from the osmotic device. The device releases active ingredient by fluid being imbibed through the semipermeable wall into the compartment at a rate determined by the permeability of the semipermeable wall and the resulting osmotic pressure gradient across the semipermeable wall thereby dispensing the drug through the passageway or orifice in the device. The dual compartment osmotic device of the present invention may provide several advantages over the monocompartment osmotic devices in delivering drugs with solubility extremes, for example, achieving zero order delivery kinetics and delivery of substantially all the drug into the target environment.
- [11] It has now been found that using polyethylene oxide with a molecular weight of 4,000,000 or lower, alone or in combination with other polymers in the push layer, results in substantially zero order release characteristics over a prolonged period of time. This reduces the fluctuations of the drug concentration level in the blood and the unwanted side effect associated with the therapy.
- [12] Summary of the Invention
- [13] In one general aspect there is provided a dual compartment osmotic delivery device. The device includes: a core comprising a drug layer, which includes one or more active ingredients, one or more gelling agents and, optionally, one or more pharmaceutically acceptable excipients; a push layer comprising polyethylene oxide having molecular weight of about 4,000,000 or lower and, optionally, one or more pharmaceutically

acceptable excipients; a semipermeable membrane surrounding the core; and at least one passageway through the semipermeable membrane into the drug layer.

- [14] Embodiments of the present invention may include one or more of the following features. For example, the active ingredient may be one or more of doxazosin, glipizide, isradipine, nifedipine, oxycodone, and methylphenidate.
- [15] The doxazosin may be co-processed doxazosin. The co-processed doxazosin may include doxazosin and one or more wetting agents. The doxazosin may be a salt of doxazosin. The wetting agent may be one or more of polyethylene glycol, polyvinyl pyrrolidone, hydroxy propyl methyl cellulose and acrylate of methacrylate polymers.
- [16] The co-processed doxazosin may be doxazosin mesylate, and polyethylene glycol.
- [17] The gelling agents may be one or more of polyethylene oxide, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium alginate, guar gum, and xanthan gum. The polyethylene oxide may have a molecular weight of 200,000.
- [18] The pharmaceutically acceptable excipients may be one or more of binders, osmotic agents, wetting agents, and lubricants. The binder may be one or more of polyvinyl pyrrolidone, pregelatinised starch and hydroxypropyl methylcellulose.
- [19] The osmotic agent may be one or more of lactose, mannitol, sorbitol, sodium chloride, potassium chloride, magnesium chloride, sodium benzoate, sodium citrate, and glycine. The wetting agent may be one or more of polyethylene glycol, propylene glycol, poloxamer, and polyoxyethylene sorbitan esters. The lubricant may be one or more of magnesium stearate, zinc stearate, talc, and colloidal silicon dioxide.
- [20] The osmotic delivery device may also include one or more osmopolymers in the push layer. The osmopolymer may be one or more of polyacrylic polymers, polymers of N-vinyl lactams, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, cross linked carboxymethylcellulose, sodium starch glycolate, sodium alginate, guar gum, xanthan gum, and copolymers of acrylic acid cross linked with a polyalkenyl polyether.
- [21] The osmotic delivery device may also include one or more non-functional coating layers below and/or above the semipermeable membrane.
- [22] In another general aspect there is provided a process for the preparation of a dual compartment osmotic delivery device. The process includes: mixing one or more active ingredients, one or more gelling agents and, optionally, one or more pharmaceutically acceptable excipients to obtain a drug layer blend; mixing polyethylene oxide having molecular weight of about 4,000,000 or lower, optionally one or more osmopolymers and, optionally, one or more pharmaceutically acceptable excipients to obtain a push layer blend; compressing the drug layer blend and the push layer blend into bilayered tablet to obtain a core; coating the core with a semipermeable

membrane; and drilling a passageway through the semipermeable membrane into the drug layer.

- [23] Embodiments of the present invention may include one or more of the following features. For example, the active ingredient may be one or more of doxazosin, glipizide, isradipine, nifedipine, oxycodone, and methylphenidate.
- [24] The doxazosin may be co-processed doxazosin. The co-processed doxazosin may include doxazosin and one or more wetting agents.
- [25] In another general aspect there is provided a method of treating hypertension and/or benign prostatic hyperplasia in a mammal in need thereof. The method includes administering a dual compartment osmotic delivery device. The osmotic delivery device includes: a core comprising a drug layer comprising doxazosin, one or more gelling agents and, optionally, one or more pharmaceutically acceptable excipients; and a push layer comprising polyethylene oxide having molecular weight of about 4,000,000 or lower and, optionally, one or more pharmaceutically acceptable excipients; a semipermeable membrane surrounding the core; and at least one passageway through the semipermeable membrane into the drug layer.
- [26] The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.
- [27] Detailed Description of the Invention
- [28] The present invention provides a dual compartment osmotic delivery device. The device includes a core that includes two layers. First, the core includes a drug layer that includes an active ingredient, one or more gelling agents, and optionally, one or more pharmaceutically acceptable excipients. Second, the core includes a push layer that includes polyethylene oxide having a molecular weight of about 4,000,000 or lower and, optionally, one or more pharmaceutically acceptable excipients. The core is surrounded by a semipermeable membrane and at least one passageway is constructed through the semipermeable membrane into the drug layer to deliver the active ingredient into the target environment.
- [29] The osmotic delivery device may further include one or more osmopolymers in the push layer. The osmotic delivery device may also include one or more non-functional coating layers below or above the semipermeable membrane.
- [30] The active ingredient may include one or more of doxazosin, glipizide, isradipine, nifedipine, oxycodone, methylphenidate or any other water soluble or insoluble drug. The active ingredient may be in the form of racemate, single enantiomer, salt, ester, solvate or mixtures thereof. For example, doxazosin mesylate may be used. The active ingredient may be used alone or may co-processed with other excipients like wetting agents.

- [31] The term 'co-processed doxazosin' includes a mixture of doxazosin and one or more wetting agents. Suitable wetting agents include one or more of polyethylene glycol, polyvinyl pyrrolidone, hydroxy propyl methylcellulose, acrylate of methacrylate polymers and mixtures thereof. For example, polyethylene glycol may be used. Any wetting agent capable of increasing the dissolution rate and/or solubility of doxazosin in comparison to that without a wetting agent may be used in the present invention.
- [32] The push layer includes one or more osmopolymers with a molecular weight of less than 4,000,000. Suitable osmopolymer include one or more of polyethylene oxide, polyacrylic polymers, polymers of N-vinyl lactams, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, cross linked carboxymethylcellulose, sodium starch glycolate, sodium alginate, guar gum, xanthan gum, copolymers of acrylic acid cross linked with a polyalkenyl polyether and mixtures thereof. An example of a suitable polyethylene oxide for use in the push layer includes the polyethylene marketed by Dow under the trade name POLYOX™. It is available in various grades depending on its molecular weight, which may range from about 100,000 to about 8,000,000. Examples of suitable grades of polyethylene oxide that may be used in the push layer include POLYOX™ WSR N-80 (MW - 200,000), WSR N-750 (MW - 300,000), WSR-205 (MW - 600,000), WSR-1105 (MW - 900,000), WSR N-12K (MW - 1,000,000), WSR N-60K (MW - 2,000,000) and WSR-301 (MW - 4,000,000). Combinations may be operable.
- [33] The drug layer includes one or more gelling agents. Suitable gelling agents include polyethylene oxide, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium alginate, guar gum, xanthan gum and mixtures thereof. The molecular weight of the gelling agent may be lower than that of the osmopolymer used in the push layer. For example, the gelling agent may be polyethylene oxide having a molecular weight of about 200,000 such as POLYOX™ WSR N-80.
- [34] Suitable pharmaceutically acceptable excipients include one or more of binders, osmotic agents, diluents, lubricants, wetting agents or solubilizing agents, absorption enhancers, emulsifiers, surfactants, swelling agents, pH modifiers, buffering agents, and coloring agents.
- [35] Suitable binders include one or more of polyvinyl pyrrolidone, pregelatinised starch, and hydroxypropyl methylcellulose.
- [36] Suitable osmotic agents may be any osmotically effective solute that is soluble in water and capable of exhibiting an osmotic pressure gradient across the wall against the external fluids. Suitable osmotic agents include one or more of lactose, mannitol, sorbitol, sodium chloride, potassium chloride, magnesium chloride, sodium benzoate, sodium citrate, glycine, and mixtures thereof.

- [37] Suitable lubricants or glidants include one or more of magnesium stearate, zinc stearate, talc, and colloidal silicon dioxide.
- [38] Suitable wetting agents or solubilizing agents include one or more of polyethylene glycol, propylene glycol, poloxamer, polyoxyethylene sorbitan esters, and mixtures thereof.
- [39] Suitable coloring agents include any FDA approved colors for oral use.
- [40] The semipermeable membrane may include one or more semipermeable membrane-forming polymers and, optionally, one or more coating additives. Suitable semipermeable membrane-forming polymers include one or more of cellulose derivatives, cellulose acetate, cellulose triacetate, agar acetate, amylose acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulphonate, cellulose acetate butyl sulphonate, cellulose acetate propionate, cellulose acetate diethylamino-acetate, cellulose acetate octate, cellulose acetate laurate, cellulose acetate p-toluenesulphonate, cellulose acetate butyrate, ethyl cellulose, polymeric epoxides, copolymers of alkylene oxides and alkyl glycidyl ethers, polyglycols, polylactic acid derivatives, and copolymers of acrylic acid ethyl ester and methacrylic acid methyl ester.
- [41] For example, the semipermeable membrane-forming polymer may be cellulose acetate. The semipermeable membrane-forming polymer may be a combination of cellulose acetates having different degrees of acetylation. The semipermeable membrane may be present at a concentration range from about 8% to about 20% w/w of the core or it may be present at a concentration range from about 10% to about 18% w/w.
- [42] Suitable coating additives include one or both of plasticizers and water soluble polymers. Suitable plasticizers include one or more of polyethylene glycol, triethyl citrate, dibutyl sebacate, triethyl phosphate, diethyl tartrate and castor oil. Suitable water soluble polymers include one or more of hydroxypropyl methylcellulose, hydroxypropyl cellulose and polyvinyl pyrrolidone.
- [43] The core of the osmotic delivery device is preferably in the form of tablets. The tablets may be prepared by any conventional tableting technique including direct compression, wet granulation or dry granulation. The tablets may be optionally coated with a non-functional coating below and/or above the semipermeable membrane.
- [44] The passageway through the semipermeable membrane may be any orifice, port, hole or opening that may be created manually or by laser drilling.
- [45] The following examples are intended to illustrate the invention and should not be construed as limiting the scope of the invention in anyway.

[46] **Compositions of Co-processed doxazosin:**

[47]

	Composition of Co-processed doxazosin	Doxazosin (mg/tablet)	PEG-6000 (mg/tablet)
1	Co-processed doxazosin	8	80
2	Co-processed doxazosin	4	40

[48] * The weight of doxazosin is expressed as weight of doxazosin base.

[49] **Preparation of co-processed doxazosin:**

[50] Polyethylene glycol - PEG-6000 (based on the ratio used) was melted and doxazosin mesylate was added to it under constant stirring. After solidification of the melt, it was crushed and passed through #44 BSS. The granules obtained are further used in the formulation and referred to herein as co-processed doxazosin.

[51] **Example 1**

[52] Core composition:

[53]

Drug layer	Ingredients	mg/tab
1	Co-processed doxazosin *	98.78
2	Sodium alginate (Keltone LVCR)	150.00
3	Sorbitol	51.22
4	Polyvinylpyrrolidone	15.00
5	Magnesium stearate	3.00
6	Colloidal silicon dioxide	2.00
	Total weight of drug layer	320.00
Push layer	Ingredients	
1	Polyethylene oxide (Polyox WSR 301)	100.00
2	Sodium chloride	58.00
3	Hydroxypropylmethylcellulose (Methocel E5)	10.00
4	Red ferric oxide	0.50
5	Magnesium stearate	1.00
6	Colloidal silicon dioxide	0.50
	Total weight of push layer	170.00

[54] *Co-processed doxazosin equivalent to 8 mg of doxazosin (+10% overage is added)

[55] **Process:**

[56] 1) Co-processed Doxazosin and all the excipients of the drug layer were mixed to obtain a drug layer blend.

[57] 2) Polyethylene oxide of the push layer and all the excipients of the push layer were mixed to obtain a push layer blend.

[58] 3) Bilayer tablets were compressed with the drug layer blend and the push layer blend using 10 mm round standard concave punches with beveled edges.

[59] 4) The bilayered tablets were coated using the following semipermeable coating composition to an approximate weight gain of about 8% to about 20%.

[60] 5) The coated tablets were dried in an oven for 16 to 24 hours.

[61] 6) An orifice (0.8 mm) was drilled using a mechanical drill.

[62] **Semipermeable coating composition:**

[63]

S. No.	Ingredients	% w/w
1	Cellulose acetate 398-10 NF	80.00
2	Polyethylene glycol (PEG-4000)	20.00

[64] **Preparation of coating composition:**

[65] Cellulose acetate and polyethylene glycol 4000 were dissolved in a mixture of acetone and water (90:10) to obtain a solution with total a solid content of 4% w/w.

[66] The following examples contain co-processed doxazosin that contain 4 mg doxazosin base plus 10% overage.

[67] **Examples 2 - 4**

[68] **Core composition:**

[69]

Drug layer	Ingredients	mg/tab		
		2	3	4
1	Co-processed doxazosin	49.39	49.39	49.39
2	Polyethylene oxide (Polyox N 80)	145.00	145.00	145.00
3	Sorbitol	85.61	85.61	20.00
4	Hydroxypropylmethylcellulose (Methocel E5)	15.00	15.00	15.00
5	Magnesium stearate	3.00	3.00	3.00
6	Colloidal silicon dioxide	2.00	2.00	2.00

	Total weight of drug layer	300.00	300.00	300.00
Push layer	Ingredients			
1	Polyethylene oxide (Polyox WSR 301)	104.00	104.00	104.00
2	Sodium chloride	42.40	-	42.40
3	Sorbitol	-	42.40	-
4	Hydroxypropylmethylcellulose (Methocel E5)	10.00	10.00	10.00
5	Red ferric oxide	2.00	-	-
6	Quinoline yellow	-	2.00	-
7	Blue lake	-	-	2.00
8	Magnesium stearate	0.80	0.80	0.80
9	Colloidal silicon dioxide	0.80	0.80	0.80
	Total weight of push layer	160.00	160.00	160.00

[70]

Process:

[71]

The same process is followed as described in Example 1.

[72]

The semipermeable coating composition is same as that of Example 1.

[73]

Semipermeable coating composition for Examples 3 and 4:

[74]

S. No.	Ingredients	% w/w
1	Cellulose acetate 398-10 NF	85.00
2	Polyethylene glycol (PEG-4000)	15.00

[75]

The Same process is followed as described in Example 1 for preparation of the semipermeable coating composition.

[76]

Examples 5 and 6

[77]

Core composition:

[78]

Drug layer	Ingredients	mg/tab	
		5	6
1	Co-processed doxazosin	49.39	49.39
2	Polyethylene oxide (Polyox N 80)	145.00	145.00

3	Sorbitol	85.61	85.61
4	Hydroxypropylmethylcellulose (Methocel E5)	15.00	15.00
5	Magnesium stearate	3.00	3.00
6	Colloidal silicon dioxide	2.00	2.00
	Total weight of drug layer	300.00	300.00
Push layer	Ingredients		
1	Polyethylene oxide (Polyox WSR 301)	104.00	-
2	Polyethylene oxide (Polyox WSR 60K)	-	104.00
3	Sodium chloride	42.40	42.40
4	Hydroxypropylmethylcellulose (Methocel E5)	10.00	10.00
5	Erythrosine	2.00	-
6	Quinoline yellow	-	2.00
7	Magnesium stearate	0.80	0.80
8	Colloidal silicon dioxide	0.80	0.80
	Total weight of push layer	160.00	160.00

[79]

Process:

[80]

The same process is followed as described in Example 1.

[81]

The semipermeable coating composition is the same as that of Example 3 and the tablets were coated to a weight gain of 12% to 13% w/w.

[82]

Table 1

[83]

The coated tablets were subjected to dissolution in a USP II apparatus, 50 rpm, 37±0.5°C in pH 6.8 buffer, 0.5% sodium lauryl sulphate, the results of which are as follows:

[84]

Time (Hours)	% release	
	Example 5	Example 6
0	0	0
2	4	3
4	13	10

6	25	21
8	36	29
10	51	41
12	68	54
16	95	86
20	99	92
24	102	97

[85]

Examples 7 - 9

[86]

Core composition:

[87]

Drug layer	Ingredients	mg/tab		
		7	8	9
1	Co-processed doxazosin	49.39	49.39	49.39
2	Polyethylene oxide (Polyox N 80)	145.00	145.00	145.00
3	Sorbitol	85.61	85.61	85.61
4	Hydroxypropylmethylcellulose (Methocel E5)	15.00	15.00	15.00
5	Magnesium stearate	3.00	3.00	3.00
6	Colloidal silicon dioxide	2.00	2.00	2.00
	Total weight of drug layer	300.00	300.00	300.00
Push layer	Ingredients			
1	Polyethylene oxide (Polyox WSR 60K)	89.00	74.00	59.00
2	Guar gum (Stamulcol ULV 500)	15.00	30.00	45.00
3	Sodium chloride	42.40	42.40	42.40
4	Hydroxypropylmethylcellulose (Methocel E5)	10.00	10.00	10.00
5	Quinoline yellow	2.00	2.00	2.00
6	Magnesium stearate	0.80	0.80	0.80
7	Colloidal silicon dioxide	0.80	0.80	0.80

	Total weight of push layer	160.00	160.00	160.00
--	-----------------------------------	---------------	---------------	---------------

[88]

Process:

[89]

The same process is followed as described in Example 1.

[90]

The semipermeable coating composition is the same as that of Example 3.

[91]

Examples 10 - 12

[92]

Core composition:

[93]

Drug layer	Ingredients	mg/tab		
		10	11	12
1	Co-processed doxazosin	49.39	49.39	49.39
2	Polyethylene oxide (Polyox N 80)	145.00	145.00	145.00
3	Sorbitol	85.61	85.61	85.61
4	Hydroxypropylmethylcellulose (Methocel E5)	15.00	15.00	15.00
5	Magnesium stearate	3.00	3.00	3.00
6	Colloidal silicon dioxide	2.00	2.00	2.00
	Total weight of drug layer	300.00	300.00	300.00
Push layer	Ingredients			
1	Polyethylene oxide (Polyox WSR 60K)	89.00	74.00	59.00
2	Sodium starch glycolate (Primogel)	15.00	30.00	45.00
3	Sodium chloride	42.40	42.40	42.40
4	Hydroxypropylmethylcellulose (Methocel E5)	10.00	10.00	10.00
5	Quinoline yellow	2.00	2.00	2.00
6	Magnesium stearate	0.80	0.80	0.80
7	Colloidal silicon dioxide	0.80	0.80	0.80
	Total weight of push layer	160.00	160.00	160.00

[94]

Process:

[95] The same process is followed as described in Example 1.

[96] The semipermeable coating composition is the same as that of Example 3.

[97] **Example 13**

[98] **Core composition:**

[99]

Drug layer	Ingredients	mg/tab
1	Doxazosin mesylate	4.4
2	Polyethylene oxide (Polyox N 80)	189.99
3	Sorbitol	85.61
4	Hydroxypropylmethylcellulose	15.00
5	Magnesium stearate	3.00
6	Colloidal silicon dioxide	2.00
	Total weight of drug layer	300.00
Push layer	Ingredients	
1	Polyethylene oxide (Polyox WSR 60K)	59.00
2	Sodium starch glycolate (Primogel)	45.00
3	Sodium chloride	42.40
4	Hydroxypropylmethylcellulose	10.00
5	Quinoline yellow	2.00
6	Magnesium stearate	0.80
7	Colloidal silicon dioxide	0.80
	Total weight of push layer	160.0

[100] **Process:**

[101] The same process is followed as described in Example 1.

[102] The semipermeable coating composition is the same as that of Example 3.

[103] **Examples 14 - 17**

[104] **Core composition:**

[105]

Drug layer	Ingredients	mg/tab			
		14	15	16	17

1	Co-processed doxazosin*	49.39	49.39	49.39	49.39
2	Polyethylene oxide (Polyox N 80)	145.00	145.00	145.00	145.00
3	Sorbitol	85.61	85.61	85.61	85.61
4	Hydroxypropylmethylcellulose (Methocel E5)	15.00	15.00	15.00	15.00
5	Magnesium stearate	3.00	3.00	3.00	3.00
6	Colloidal silicon dioxide	2.00	2.00	2.00	2.00
	Total weight of drug layer	300.00	300.00	300.00	300.00
Push layer	Ingredients				
1	Polyethylene oxide (Polyox WSR 301)	74.00	74.00	74.00	74.00
2	Guar gum	30.00	-	-	-
3	Sodium starch glycolate (Primogel)	-	30.00	-	-
4	Xanthan gum	-	-	30.00	-
5	Hydroxypropylmethylcellulose (Methocel K 15 MCR)	-	-	-	30.00
6	Sodium chloride	42.40	42.40	42.40	42.40
7	Hydroxypropylmethylcellulose (Methocel E5)	10.00	10.00	10.00	10.00
8	Red ferric oxide	2.00	2.00	2.00	2.00
9	Magnesium stearate	0.80	0.80	0.80	0.80
10	Colloidal silicon dioxide	0.80	0.80	0.80	0.80
	Total weight of push layer	160.00	160.00	160.00	160.00

[106] * Equivalent to 4.4 mg of Doxazosin

[107] **Process:**

[108] The same process is followed as described in Example 1.

[109] The semipermeable coating composition is the same as that of Example 3 and the tablets were coated to a weight gain of 12% to 14% w/w.

[110] **Table 2**

[111] The coated tablets were subjected to dissolution in a USP II apparatus, 50 rpm,

37±0.5°C in pH 6.8 buffer, 0.5% sodium lauryl sulphate, the results of which are provided below as follows:

[112]

Time (Hours)	% release			
	Example 14	Example 15	Example 16	Example 17
0	0	0	0	0
2	3	3	4	2
4	14	16	13	10
6	31	32	25	20
8	46	46	35	28
12	81	86	66	55
16	108	111	94	86
24	111	115	107	100

[113]

Example 18

[114]

Core composition:

[115]

Drug layer	Ingredients	mg/tab
1	Doxazosin mesylate	5.4
2	Polyethylene glycol-6000	44.01
3	Polyethylene oxide (Polyox N 80)	144.99
4	Sorbitol	84.60
5	Polyvinylpyrrolidone (PVP K30)	15.00
6	Magnesium stearate	3.00
7	Colloidal silicon dioxide	2.01
8	Talc	0.99
	Total weight of drug layer	300.00
Push layer	Ingredients	
1	Polyethylene oxide (Polyox WSR 60K)	74.00
2	Sodium starch glycolate (Primogel)	30.00
3	Sodium chloride	42.40

4	Polyvinylpyrrolidone (PVP K30)	10.00
5	Red ferric oxide	1.50
6	Magnesium stearate	0.80
7	Colloidal silicon dioxide	0.80
8	Talc	0.5
	Total weight of push layer	160.0

[116] **Process:**

[117] 1) Doxazosin mesylate, polyethylene glycol 6000, polyethylene oxide (Polyox N 80) and sorbitol were mixed to obtain a mixture.

[118] 2) The mixture of step 1 was granulated with polyvinylpyrrolidone solution, dried and sized through BSS #22 followed by blending with magnesium stearate, colloidal silicon dioxide, and talc to obtain a drug layer blend.

[119] 3) Polyethylene oxide of the push layer, sodium starch glycolate, sodium chloride, and red ferric oxide were mixed to obtain a mixture.

[120] 4) The mixture of step 3 was granulated with polyvinylpyrrolidone solution, dried and sized through BSS #22 followed by blending with magnesium stearate, colloidal silicon dioxide, and talc to obtain a push layer blend.

[121] 5) Bilayer tablets were compressed with the drug layer blend and the push layer blend using 10 mm round standard concave punches with beveled edges.

[122] 6) The bilayered tablets were coated using the following coating composition to an approximate weight gain of about 0.5% to about 2% w/w.

[123]

S. No.	Ingredients	% w/w
1	Hydroxypropylmethylcellulose (Methocel E-5)	80
2	Polyethylene glycol (PEG-4000)	20

[124] Hydroxypropylmethylcellulose and polyethylene glycol-4000 were dissolved in isopropyl alcohol:methylene chloride (60:40) to obtain a solution with around 5% solids.

[125] 7) The above coated tablets were further coated with the semipermeable coating composition of Example 3 to a weight gain of 13.51% w/w (Example 18A), 15.24%w/w (Example 18B) and 17.42% w/w (Example 18C).

[126] 8) The coated tablets were dried in an oven for 16 to 24 hours.

[127] 9) An orifice (0.8 mm) was drilled using a mechanical drill.

[128] **Table 3**

[129] The coated tablets were subjected to dissolution in a USP II apparatus, 50 rpm, $37\pm 0.5^{\circ}\text{C}$ in pH 6.8 buffer, 0.5% sodium lauryl sulphate, the results of which are described below as follows:

[130]

Time (Hours)	% release		
	Example 18A	Example 18B	Example 18C
0	0	0	0
2	4	2	2
4	15	9	9
6	32	21	16
8	47	34	30
12	81	56	56
16	106	87	84
24	107	106	109

[131] **Example 19**

[132] **Core composition:**

[133]

Drug layer	Ingredients	mg/tab
1	Co-processed doxazosin*	49.38
2	Polyethylene oxide (Polyox N 80)	144.99
3	Sorbitol	84.60
4	Polyvinylpyrrolidone (PVP K30)	15.00
5	Magnesium stearate	3.00
6	Colloidal silicon dioxide	2.01
7	Talc	0.99
	Total weight of drug layer	300.00
Push layer	Ingredients	
1	Polyethylene oxide (Polyox WSR 60K)	74.00
2	Sodium starch glycolate (Primogel)	30.00
3	Sodium chloride	42.40

4	Polyvinylpyrrolidone (PVP K30)	10.00
5	Red ferric oxide	1.50
6	Magnesium stearate	0.80
7	Colloidal silicon dioxide	0.80
8	Talc	0.5
	Total weight of push layer	160.0

[134] **Process:**

[135] The same process is followed as described in Example 18.

[136] The semipermeable coating composition is the same as that of Example 3 and the tablets were coated to a weight gain of 14.23% w/w (Example 19A), 15.06%w/w (Example19B) and 15.68% w/w (Example 19C).

[137] **Table 4**

[138] The coated tablets were subjected to dissolution in a USP II apparatus, 50 rpm, $37 \pm 0.5^\circ\text{C}$ in pH 6.8 buffer, 0.5% sodium lauryl sulphate, the results of which are described below as follows:

[139]

Time (Hours)	% release		
	Example 19A	Example 19B	Example 19C
0	0	0	0
2	4	4	3
4	15	15	13
6	31	29	24
8	46	42	36
12	76	68	60
16	99	94	87
24	107	105	104

[140] **Examples 20 and 21**

[141] **Core composition:**

[142]

Drug layer	Ingredients	mg/tab	
		20	21
1	Co-processed doxazosin*	47.15	47.15

2	Polyethylene oxide (Polyox N 80)	148.85	148.85
3	Polyvinylpyrrolidone (PVP K30)	10.00	10.00
4	Magnesium stearate	2.00	2.00
5	Colloidal silicon dioxide	1.00	1.00
6	Talc	1.00	1.00
	Total weight of drug layer	210.00	210.00
Push layer	Ingredients		
1	Polyethylene oxide (Polyox WSR 60K)	89.40	-
2	Polyethylene oxide (Polyox WSR 301)	-	89.40
3	Sodium chloride	40.00	40.00
4	Polyvinylpyrrolidone (PVP K30)	7.00	7.00
5	Red ferric oxide	1.50	1.50
6	Magnesium stearate	0.80	0.80
7	Colloidal silicon dioxide	0.80	0.80
8	Talc	0.5	0.5
	Total weight of push layer	140.0	140.0

[143] *Equivalent to 4.2 mg of Doxazosin

[144] **Process:**

[145] The same process is followed as described in Example 1.

[146] The semipermeable coating composition is the same as that of Example 3 and the tablets were coated to a weight gain of about 14% to about 15% w/w.

[147] **Table 5**

[148] The coated tablets were subjected to dissolution in a USP II apparatus, 50 rpm, 37±0.5°C in pH 6.8 buffer, 0.5% sodium lauryl sulphate, the results of which are described below as follows:

[149]

Time (Hours)	% release	
	Example 20	Example 21
0	0	0

2	5	4
4	20	19
6	36	35
8	51	48
12	82	74
16	95	93
24	98	97

[150] While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

Claims

- [1] A dual compartment osmotic delivery device comprising:
- a) a core comprising:
 - 1) a drug layer comprising one or more active ingredients, one or more gelling agents and, optionally, one or more pharmaceutically acceptable excipients;
 - 2) a push layer comprising polyethylene oxide having a molecular weight of about 4,000,000 or lower and, optionally, one or more pharmaceutically acceptable excipients;
 - b) a semipermeable membrane surrounding the core; and
 - c) at least one passageway through the semipermeable membrane into the drug layer.
- [2] The osmotic delivery device of claim 1, wherein the active ingredient comprises one or more of doxazosin, glipizide, isradipine, nifedipine, oxycodone, and methylphenidate.
- [3] The osmotic delivery device of claim 2, wherein the doxazosin is co-processed doxazosin.
- [4] The osmotic delivery device of claim 3, wherein the co-processed doxazosin comprises doxazosin and one or more wetting agents.
- [5] The osmotic delivery device of claim 4, wherein the doxazosin comprises a salt of doxazosin.
- [6] The osmotic delivery device of claim 4, wherein the wetting agent comprises one or more of polyethylene glycol, polyvinyl pyrrolidone, hydroxy propyl methyl cellulose, and acrylate of methacrylate polymers.
- [7] The osmotic delivery device of claim 4, wherein the co-processed doxazosin comprises doxazosin mesylate and polyethylene glycol.
- [8] The osmotic delivery device of claim 1, wherein the gelling agents comprise one or more of polyethylene oxide, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium alginate, guar gum, and xanthan gum.
- [9] The osmotic delivery device of claim 8, wherein the polyethylene oxide has a molecular weight of 200,000.
- [10] The osmotic delivery device of claim 1, wherein the pharmaceutically acceptable excipients comprise one or more of binders, osmotic agents, wetting agents, and lubricants.
- [11] The osmotic delivery device of claim 10, wherein the binder comprises one or more of polyvinyl pyrrolidone, pregelatinised starch, and hydroxypropyl methyl-

cellulose.

- [12] The osmotic delivery device of claim 10, wherein the osmotic agent comprises one or more of lactose, mannitol, sorbitol, sodium chloride, potassium chloride, magnesium chloride, sodium benzoate, sodium citrate, and glycine.
- [13] The osmotic delivery device of claim 10, wherein the wetting agent comprises one or more of polyethylene glycol, propylene glycol, poloxamer, and polyoxyethylene sorbitan esters.
- [14] The osmotic delivery device of claim 10, wherein the lubricant comprises one or more of magnesium stearate, zinc stearate, talc, and colloidal silicon dioxide.
- [15] The osmotic delivery device of claim 1, further comprising one or more osmopolymers in the push layer.
- [16] The osmotic delivery device of claim 15, wherein the osmopolymer comprises one or more of polyacrylic polymers, polymers of N-vinyl lactams, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, cross linked carboxymethylcellulose, sodium starch glycolate, sodium alginate, guar gum, xanthan gum, and copolymers of acrylic acid cross linked with a polyalkenyl polyether.
- [17] The osmotic delivery device of claim 1, further comprising one or more non-functional coating layers below and/or above the semipermeable membrane.
- [18] A process for the preparation of a dual compartment osmotic delivery device, the process comprising:
- a) mixing one or more active ingredients, one or more gelling agents and, optionally, one or more pharmaceutically acceptable excipients to obtain a drug layer blend;
 - b) mixing polyethylene oxide having molecular weight of about 4,000,000 or lower, optionally one or more osmopolymers and, optionally, one or more pharmaceutically acceptable excipients to obtain a push layer blend;
 - c) compressing the drug layer blend and the push layer blend into bilayered tablet to obtain a core;
 - d) coating the core with a semipermeable membrane; and
 - e) drilling a passageway through the semipermeable membrane into the drug layer.
- [19] The process of claim 18, wherein the active ingredient comprises one or more of doxazosin, glipizide, isradipine, nifedipine, oxycodone and methylphenidate.
- [20] The process of claim 19, wherein the doxazosin is co-processed doxazosin.
- [21] The process of claim 20, wherein the co-processed doxazosin comprises doxazosin and one or more wetting agents.

- [22] A method of treating hypertension and/or benign prostatic hyperplasia in a mammal in need thereof, the method comprising administering a dual compartment osmotic delivery device comprising:
- a) a core comprising:
 - 1) a drug layer comprising doxazosin, one or more gelling agents and, optionally, one or more pharmaceutically acceptable excipients;
 - 2) a push layer comprising polyethylene oxide having molecular weight of about 4,000,000 or lower and, optionally, one or more pharmaceutically acceptable excipients;
 - b) a semipermeable membrane surrounding the core; and
 - c) at least one passageway through the semipermeable membrane into the drug layer.