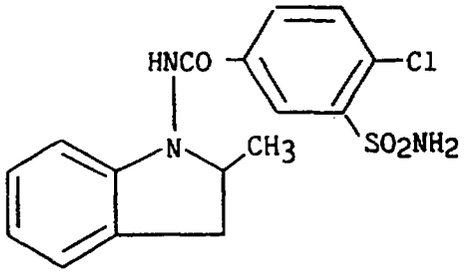
The present invention relates to a matrix tablet that permits the sustained release of indapamide, which ensures that blood levels are consistent and constant after absorption of the galenic form by the oral route.

Indapamide, the compound of formula (I):



(I),

is a non-thiazide sulphamide compound having anti-hypertensive properties at the doses customarily administered to humans.

Hitherto, indapamide has been administered orally in a dose of 2.5 mg per day by means of an immediate release form.

However, in certain patients an immediate release form may lead to large peaks in blood level being obtained. With a sustained release form it is possible to avoid those peaks in blood level and to obtain a consistent concentration in the blood in humans. This makes it possible to reduce the undesirable effects which may occur as a result of the "peak effect", accompanied by disorders of the hydroelectric and metabolic type associated with variations in the plasma levels of the active ingredient.

A sustained release form for indapamide therefore permits a better therapeutic index in the treatment of essential arterial hypertension.

To that end it is necessary to ensure that the release is sustained over time, in a perfectly controlled manner. The rate of release must be reproducible and correlated with the concentrations in the blood observed after administration.

Of the mechanisms that can be used to control the diffusion of a soluble active ingredient, one principal method may be mentioned, which is diffusion of the active ingredient through a gel formed after swelling of a hydrophilic polymer that has been brought into contact with the dissolution liquid (*in vitro*) or with gastrointestinal fluid (*in vivo*).

Many polymers have been described as being capable of permitting the formation of the gel. The main ones are cellulose compounds, especially cellulose ethers, such as hydroxypropylcellulose, hydroxymethylcellulose, methylcellulose and methylhydroxypropylcellulose, and of the various commercial grades of those ethers, those having relatively high viscosities. It must be noted that the systems described do not in theory allow a zero order to be obtained in the equation of the kinetics of release.

The manufacturing processes currently employed for the manufacture of such matrix tablets are either direct compression, after mixing of the various excipients and the active ingredient or ingredients, or moist granulation.

The matrix tablet described in the present invention combines two polymers from different chemical families in a novel manner, allowing the active ingredient to be released in a perfectly controlled manner. Moreover, that combination adapts itself perfectly to the physico-chemical properties of indapamide.

The controlled release is linear for a period of more than 8 hours and is such that 50% of the total quantity of indapamide is released between 5 and 14 hours. Furthermore, the matrix tablet according to the invention allows sustained release of indapamide to be obtained to give blood levels in humans of from 20 to 80 ng/ml, 24 hours at most after administration of the tablet. The unit dose can thus vary according to the age and weight of the patient and the nature and severity of the disorder. In general, it ranges from 1 to 2.5 mg for one daily treatment.

The first polymer is a high-viscosity methylhydroxy-propylcellulose, and the second is a polyvidone. Combining those two polymers allows a linear kinetics of release (zero order) to be obtained *in vitro* over a period of more than 8 hours. The percentage of cellulose-derived polymer is from 30 to 50% of the total mass of the tablet, and the percentage of the polyvidone compound is from 2 to 10% of the total mass of the tablet.

The two polymers are used separately in the tablet in order to control the release of the active ingredient in a reproducible manner. A novel manufacturing process has been developed so that each polymer used in the formulation can play its part in the most effective manner

possible with the advantages of the two processes, moist granulation and direct compression.

Moist granulation is carried out with the polyvidone in order to create around the active ingredient a hydrophilic environment favourable to good dissolution thereof, and also so as to obtain a unit dose that is as consistent as possible, the indapamide content of the finished tablet being approximately 1%. To that end a hydrophilic diluent, lactose, is used.

After the granulation step, a mixture for direct compression is prepared, then compressed.

The following Examples illustrate the invention but do not limit it in any way. The sustained release tablets are prepared by the following manufacturing process:

Step A : Mixing the indapamide, the polyvidone and the lactose, and then moistening the mixture with an aqueous alcoholic solution. The prepared moist mass is then granulated, dried and then graded in order to obtain a granulate whose physical characteristics allow good filling of the moulds of a rapid compression machine.

Step B : Mixing the granulate obtained in Step A with the methylhydroxypropylcellulose.

Step C : Lubricating the mixture obtained in Step B with colloidal silica and magnesium stearate.

Step D : Compressing the lubricated mixture obtained in Step C in a rotary compression machine, so as to

obtain tablets having a hardness, measured by diametral crushing, of approximately from 60 to 75 N.

EXAMPLE 1:

A sustained release tablet (SR 1) is prepared using the formulation given in Table 1, following the procedure described in Steps A to D.

Table 1 : Unit formulation for tablet SR 1

Compound	Quantity (mg)
Indapamide	2.5
Lactose	114.9
Polyvidone	6.2
Methylhydroxypropylcellulose	59.0
Magnesium stearate	2.0
Colloidal silica	0.4

The profile of dissolution *in vitro* for this form (SR 1) is shown in Figure 1 (attached).

The concentrations of indapamide in the blood were measured in six patients following administration of tablet SR 1 or of an immediate release tablet (IR). The average curve is given in Figure 2 (attached).

EXAMPLE 2:

A sustained release tablet (SR 2) is prepared using the formulation given in Table 2, following the procedure described in Steps A to D.

Table 2 : Unit formulation for tablet SR 2

Compound	Quantity (mg)
Indapamide	2.5
Lactose	114.9
Polyvidone	6.2
Methylhydroxypropylcellulose	74.0
Magnesium stearate	2.0
Colloidal silica	0.4

The profile of dissolution *in vitro* of this form is shown in Figure 3 (attached).

The concentrations of indapamide in the blood were measured in six patients following administration of tablet SR 2 or of an immediate release form (IR). The average curve is given in Figure 4 (attached).

The fact that the formulations described in Examples 1 and 2 differ only in the quantity of methylhydroxypropyl-cellulose shows that it is simple to control the kinetics of dissolution of indapamide *in vitro*. The relation with the blood kinetics measured *in vivo* is very good. Two significantly different blood kinetics are found.

EXAMPLES 3 TO 5:

Three sustained release tablets (SR 3, SR 4 and SR 5) are prepared using the formulations given in Table 3, following the procedure described in Steps A to D.

Table 3 : Unit formulation for tablets SR 3, SR 4 and SR 5

Tablet	SR 3	SR 4	SR 5
	Quantity		
	(mg)	(mg)	(mg)
Indapamide	2.0	2.0	2.0
Lactose	115.4	113.0	113.0
Polyvidone	6.2	8.6	8.6
Methylhydroxypropyl-cellulose	74.0	74.0	59.0
Magnesium stearate	2.0	2.0	2.0
Colloidal silica	0.4	0.4	0.4

The profiles of dissolution *in vitro* of these three forms are shown in Figure 5 (attached). They show that by altering the concentration of each polymer in the formulation it is possible to modulate the release of the active ingredient.

CLAIMS for Contracting States: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. Matrix tablet for the sustained release of indapamide, characterised in that the sustained release is controlled by the use of methylhydroxypropylcellulose and polyvidone, the percentages of which are from 30 to 50% and from 2 to 10%, respectively, of the total mass of the tablet.

2. Indapamide matrix tablet according to claim 1, characterised in that the percentages of the cellulose and polyvidone compounds permit the sustained release of indapamide in a manner that is linear for a period of at least eight hours.

3. Indapamide matrix tablet according to claim 1, characterised in that the percentages of the cellulose and polyvidone compounds permit the release of 50% of the total quantity of indapamide within a period of from 5 to 14 hours.

4. Indapamide matrix tablet according to claim 1, characterised in that the percentages of the cellulose and polyvidone compounds permit the sustained release of indapamide to give blood levels in humans of from 20 to 80 ng/ml, 24 hours at most after administration of the tablet by the oral route.

5. Process for the preparation of an indapamide matrix tablet according to claim 1, characterised in that there are used both a moist granulation technique and a direct compression technique, comprising the following steps:

Step (A): mixing the indapamide, the polyvidone and lactose, and then moistening the mixture with an aqueous alcoholic solution to yield a moist mass which is then granulated, dried and then graded, so as to obtain a granulate whose physical characteristics allow good filling of the moulds of a rapid compression machine;
Step (B): mixing the granulate obtained in Step A with the methylhydroxypropylcellulose;
Step (C): lubricating the mixture obtained in Step B with colloidal silica and magnesium stearate;
Step (D): compressing the lubricated mixture obtained in Step C in a rotary compression machine, so as to obtain tablets having a hardness, measured by diametral crushing, of approximately from 60 to 75 N.

6. Indapamide matrix tablet according to any one of claims 1 to 4 for use in the treatment of essential arterial hypertension.