So long as it is accepted in the art, any hard capsule may be employed in the capsule formulation of the present invention. The hard capsule useful in the present invention may be made of gelatin, hypromellose, pullulan (*e.g.*, NP Caps^{TM}, Capsugel), or polyvinyl alcohol.

So long as it is accepted for typical medicines, any capsule size may be employed for the hard capsule available in the capsule formulation of the present invention. In the pharmaceutical field, capsule sizes, *i.e.*, internal volumes of capsules, can be discriminated by accompanying capsule size numbers. For example, a volume ozf 0.95 mL is denoted by capsule size 00, 0.68 mL by capsule size 0, 0.47 mL by capsule size 1, 0.37 mL by capsule size 2, 0.27 mL by capsule size 3 and 0.20 mL by capsule size 4 (refer to web-page of Suheung Capsule). Although smaller capsule sizes are better for drug compliance, capsules with size 0, 1, 2, 3 or 4 may be used in consideration of the content of the active ingredients loaded thereto. Preferred is a capsule size 1, 2 or 3.

In accordance with another aspect thereof, the present invention provides a method for preparing the pharmaceutical composite capsule formulation, comprising: 1) forming irbesartan granules or tablets comprising irbesartan or a pharmaceutically acceptable salt thereof; 2) forming HMG-CoA reductase inhibitor granules or tablets comprising a HMG-CoA reductase inhibitor or a pharmaceutically acceptable salt thereof, and an alkaline additive; and 3) loading the irbesartan granules or tablets of step 1) and the HMG-CoA reductase inhibitor granules or tablets of step 2) into a hard capsule, said ~~HMG-CoA reductase inhibitor~~irbesartan granules or tablets existing separate from said HMG-CoA reductase inhibitor granules or tablets within the capsule.

In one embodiment, the method comprises: i) granulating irbesartan or a pharmaceutically acceptable salt thereof in mixture with a pharmaceutically acceptable additive to form granules, and optionally compressing the granules into tablets; ii) granulating an HMG-CoA reductase inhibitor or a pharmaceutically acceptable salt thereof, and an alkaline additive in mixture of a pharmaceutically acceptable additive to form granules, and optionally compressing the granules into tablets; (and optionally, coating the irbesartan granules or tablets of step i) and the HMG-CoA reductase inhibitor granules or tablets of step ii)); and iii) loading the irbesartan granules or tablets of step i) and the HMG-CoA reductase inhibitor granules or tablets of step ii) into a hard capsule, such that said irbesartan granules or tablets are separated from said HMG-CoA reductase inhibitor granules or tablets within the capsule.

The steps of the preparing method of the present invention may be carried out using typical processes. In step i) or ii), the granules may be compressed into tablets using a

Table 6A

Degradation products of atorvastatin after storage in long-term condition (25°C, 60% RH) (RRT 1.81)

	Example No.	Long-term condition (months)							
		0	3	6	9	12	18	24	36
Degradation product of atorvastatin (%)	Example 5	0.07	0.09	0.09	0.11	0.12	0.14	0.16	0.18
	Comparative Example 1	0.12	0.13	0.15	0.17	0.18	0.23	0.28	0.45
	Comparative Example 2	0.1	0.1	0.09	0.12	0.13	0.14	0.17	0.19
	Comparative Example 3	0.08	0.06	0.1	0.12	0.14	0.17	0.19	0.26

Table 6B

Degradation products of ~~atorvastatin~~irbesartan after storage in acceleration condition (40°C, 75% RH) (RRT 0.8)

	Acceleration condition (month)			
	Example No.	0	3	6
Degradation product of irbesartan(%)	Example 5	0.031	0.042	0.072
	Comparative Example 1	0.031	0.035	0.062
	Comparative Example 2	0.028	0.031	0.073
	Comparative Example 3	0.044	0.073	0.161

As can be seen in Tables 6A and 6B, degradation products of atorvastatin (RRT 1.81) and irbesartan (RRT 0.8) increased in quantity with time. According to the ICH guideline for related substance, both irbesartan and atorvastatin must be degraded at a rate of 0.2% or less for 6 months in an acceleration condition or for 24 to 36 months in a long-term condition. The formulation according to the present invention was improved in stability of atorvastatin owing to the presence of the alkaline additive. With superiority in stability to the formulations of Comparative Examples 1 to 3, the formulation of the present invention was proven for the product having a shelf life of 3 or more years.

Test Example 2: Dissolution Assay of Irbesartan

Formulations of Example 5 and Comparative Examples 1 to 3 were assayed for irbesartan dissolution in the following dissolution test condition. Aprovel™ 150 mg (Sanofi-Aventis) was used as a control. The results are shown in FIG. 3.

<Dissolution test condition>

(1) Dissolution tester: PTWS-1210 (Pharmatest, Germany)

(2) Dissolution medium: 0.1 mol/L HCl

So long as it is accepted in the art, any hard capsule may be employed in the capsule formulation of the present invention. The hard capsule useful in the present invention may be made of gelatin, hypromellose, pullulan (*e.g.*, NP Caps™, Capsugel), or polyvinyl alcohol.

So long as it is accepted for typical medicines, any capsule size may be employed for the hard capsule available in the capsule formulation of the present invention. In the pharmaceutical field, capsule sizes, *i.e.*, internal volumes of capsules, can be discriminated by accompanying capsule size numbers. For example, a volume ozf 0.95 mL is denoted by capsule size 00, 0.68 mL by capsule size 0, 0.47 mL by capsule size 1, 0.37 mL by capsule size 2, 0.27 mL by capsule size 3 and 0.20 mL by capsule size 4 (refer to web-page of Suheung Capsule). Although smaller capsule sizes are better for drug compliance, capsules with size 0, 1, 2, 3 or 4 may be used in consideration of the content of the active ingredients loaded thereto. Preferred is a capsule size 1, 2 or 3.

In accordance with another aspect thereof, the present invention provides a method for preparing the pharmaceutical composite capsule formulation, comprising: 1) forming irbesartan granules or tablets comprising irbesartan or a pharmaceutically acceptable salt thereof; 2) forming HMG-CoA reductase inhibitor granules or tablets comprising a HMG-CoA reductase inhibitor or a pharmaceutically acceptable salt thereof, and an alkaline additive; and 3) loading the irbesartan granules or tablets of step 1) and the HMG-CoA reductase inhibitor granules or tablets of step 2) into a hard capsule, said irbesartan granules or tablets existing separate from said HMG-CoA reductase inhibitor granules or tablets within the capsule.

In one embodiment, the method comprises: i) granulating irbesartan or a pharmaceutically acceptable salt thereof in mixture with a pharmaceutically acceptable additive to form granules, and optionally compressing the granules into tablets; ii) granulating an HMG-CoA reductase inhibitor or a pharmaceutically acceptable salt thereof, and an alkaline additive in mixture of a pharmaceutically acceptable additive to form granules, and optionally compressing the granules into tablets; (and optionally, coating the irbesartan granules or tablets of step i) and the HMG-CoA reductase inhibitor granules or tablets of step ii)); and iii) loading the irbesartan granules or tablets of step i) and the HMG-CoA reductase inhibitor granules or tablets of step ii) into a hard capsule, such that said irbesartan granules or tablets are separated from said HMG-CoA reductase inhibitor granules or tablets within the capsule.

The steps of the preparing method of the present invention may be carried out using typical processes. In step i) or ii), the granules may be compressed into tablets using a

Table 6A

Degradation products of atorvastatin after storage in long-term condition (25°C, 60% RH) (RRT 1.81)

	Example No.	Long-term condition (months)							
		0	3	6	9	12	18	24	36
Degradation product of atorvastatin (%)	Example 5	0.07	0.09	0.09	0.11	0.12	0.14	0.16	0.18
	Comparative Example 1	0.12	0.13	0.15	0.17	0.18	0.23	0.28	0.45
	Comparative Example 2	0.1	0.1	0.09	0.12	0.13	0.14	0.17	0.19
	Comparative Example 3	0.08	0.06	0.1	0.12	0.14	0.17	0.19	0.26

Table 6B

Degradation products of irbesartan after storage in acceleration condition (40°C, 75% RH) (RRT 0.8)

	Acceleration condition (month)			
	Example No.	0	3	6
Degradation product of irbesartan(%)	Example 5	0.031	0.042	0.072
	Comparative Example 1	0.031	0.035	0.062
	Comparative Example 2	0.028	0.031	0.073
	Comparative Example 3	0.044	0.073	0.161

As can be seen in Tables 6A and 6B, degradation products of atorvastatin (RRT 1.81) and irbesartan (RRT 0.8) increased in quantity with time. According to the ICH guideline for related substance, both irbesartan and atorvastatin must be degraded at a rate of 0.2% or less for 6 months in an acceleration condition or for 24 to 36 months in a long-term condition. The formulation according to the present invention was improved in stability of atorvastatin owing to the presence of the alkaline additive. With superiority in stability to the formulations of Comparative Examples 1 to 3, the formulation of the present invention was proven for the product having a shelf life of 3 or more years.

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<Dissolution test condition>

(1) Dissolution tester: PTWS-1210 (Pharmatest, Germany)

(2) Dissolution medium: 0.1 mol/L HCl