

### FORMULATION AND DEVELOPMENT OF S-(-)-AMLODIPINE BESYLATE TABLETS TO IMPROVE THE DISSOLUTION PROFILE.

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#### ABSTRACT

The objective of the present study was to develop a tablet formulation of S-(-)- amlodipine besylate chiral separation drug, L-Type Calcium channel blocker for better management of hypertension and also suitable in the treatment diabetic hypertension patients, while reducing or avoiding undesirable adverse effects, such as headache and edema, dizziness, flushing, palpitation, fatigue, nausea, abdominal pain and somnolence which are often associated with administration of a racemic mixture of amlodipine. The R (+) enantiomer lacks or has a lower level of antihypertensive activity.

In the present study S-(-)- amlodipine besylate 5.0 mg tablets have been formulated and developed using wet granulation and direct compression techniques respectively, to provide a safe, highly effective method for treating severe hypertension while reducing undesirable adverse effects. Pre and post formulation parameters were studied for the formulated batches. The study was also carried out to design a suitable dissolution medium for S-(-)- amlodipine besylate. S-(-)- amlodipine besylate had maximum solubility in pH 1.2 and thus the most suitable media for S-(-)- amlodipine besylate dissolution studies. The dissolution profile of the formulated formulation was compared with the marketed preparation. The results indicated improved dissolution profile of formulation (WMS3). The RSD below 2% indicated insignificant batch-to-batch variation. The accelerated stability study of the optimized formulation was performed as per the ICH guidelines. The results indicated no change in optical rotation of S-(-)- amlodipine besylate.

**Keywords:** Tablet, S-(-)- amlodipine besylate, dissolution, wet granulation, direct compression.

#### INTRODUCTION

According to the World Health Organization (WHO), hypertension (high blood pressure) is the most common cardiovascular condition in the world and there are about 600 million people at risk for heart attack, stroke and cardiac failure.

High blood pressure is estimated to cause 7.1 million deaths, about 13 percent of the global fatality total. It is believed this number will grow to approximately 11 million by the year 2020. Heart disease is the leading cause of death in the U.S., accounting for nearly 740,000 deaths each year. Cardiovascular disease is also the leading cause of death in Europe, accounting for over 4

million deaths each year. Hypertension is the leading risk factor for cardiovascular and renal disease, increasing the risk of myocardial infarction, stroke, congestive heart failure, ruptured aortic aneurysm, and renal disease. It is clearly understandable that a more rational approach to diagnosing and treating high blood pressure could have a substantial impact on population morbidity and mortality, especially considering the current lack of success.

Hypertension is usually defined as a diastolic blood pressure of 90 mm Hg or higher or a systolic pressure of 140 mm Hg or higher. Most experts categorize hypertensive patients into the following two classifications: 1) Es-

sential Hypertension (80-85%). This is a synonym for "idiopathic" which denotes the underlying causes can not be determined but are certainly related to complex processes in all major organs and systems, including the heart, blood vessels, nerves, hormones, and the kidneys. 2) Secondary Hypertension (15-20%). Unlike essential hypertension, secondary hypertension has an identifiable cause and in many cases is curable. Common causes include kidney disorders (e.g., renal artery stenosis, inflammation, injury, etc.), hormonal disorders (e.g., aldosteronism, hyperthyroidism, pheochromocytoma, etc.), obesity, a sedentary lifestyle, smoking, and excessive alcohol or salt consumption (1).

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extra cellular calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The (-) isomer has been reported to be more active than the (+) isomer (2-5).

S (-) amlodipine besylate is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the administration of the racemic mixture of amlodipine. The s(-) isomer of amlodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of s (-) amlodipine as a calcium channel antagonist without the concomitant liability of adverse effects associated with the racemic mixture of amlodipine (6-7).

Since no systematic studies on design and development of s(-)- amlodipine besylate or in vitro are available in literature, we propose to develop a suitable formulation and dissolution medium to characterize in vitro release profile of s(-)- amlodipine besylate. Thus a safe, highly effective method for treating severe hypertension while reducing undesirable adverse effects with improved patient compliance and acceptance.

The dissolution profile of the formulated formulation was

compared with the marketed preparation. The results indicated improved dissolution profile of formulation WMS 3. The RSD below 2% indicated insignificant batch-to-batch variation.

## MATERIALS AND METHOD

### Materials

Amlodipine besylate was generously supplied as a gift sample by M/s Pravin Laboratories Ltd, (Moje-Jolwa, Gujarat). Lactose, M/s Dynamix India (Baramati, M.S.), Starch, M/s Tirupati Starch and Chemicals Ltd (Dhar, M.P.), and Microcrystalline cellulose (MCC) JRS Pharma (Rosenberg, Germany), All other chemicals were of analytical reagent grade and were used as received.

### Formulations of S(-)- Amlodipine besylate

The granules of microcrystalline cellulose-starch and lactose-starch were prepared in the ratio as shown in (Table 1). To arrive at an optimal formulation, preliminary data on various derived characters and physical characters of tablets were generated (Table 3). The granules were lubricated with magnesium stearate (0.5%) and talc (1%), and compressed using a Cadmach makes double rotary single punch, with oval shaped punches. The drug S(-)- amlodipine besylate was added at the lubrication stage because S(-)- amlodipine besylate has low melting point and at high temperature is chiral sensitive. The tablets had an average weight of 125 mg and each tablet contained 5 mg of S(-)- amlodipine besylate.

In order to minimize the processing steps, S(-)- amlodipine besylate tablets were prepared by direct compression technique. S(-)- amlodipine besylate was blended with directly compressible diluents like starch and microcrystalline cellulose. Crosscarmellulose (1, 1.5 and 2%) was added as disintegrating agent. The final powder blend was lubricated with 0.75% magnesium stearate and 1.5% talc and compressed as described earlier (Table 2).

### Evaluation

The tablets of S(-)- amlodipine besylate, prepared by wet granulation and direct compression techniques were evaluated for preformulation and post formulation parameters, such as hardness, friability, disintegration, content uniformity and in vitro release profile.

### Bulk and Tapped Density (Hausner's Ratio and Carr's Compressional Index)

The density parameters were determined using 10.0 g of each material in a 25 mL graduated cylinder (n = 3) (Electrolab Tap density tester USP: ETD-1020). The values were used to calculate Hausner's Ratio and Carr's Compressional Index (8, 9).

### Flowability

The flow properties of the sample were evaluated by the dynamic flow determination. The analysis was performed 3 times with 10.0 g of each sample (10).

### Solubility Study of S(-)- amlodipine besylate

Maximal solubility of S(-)- amlodipine besylate in various physiological pH (pH 1.2, pH 4.0, pH 6.8 Phosphate buffer, pH 7.4 Phosphate buffer), was studied. Excess amount of S(-)- amlodipine besylate was taken in 10 ml of the above media, in boiling test tube, and dissolved in triplicates by sonication. The maximal solubility of S(-)- amlodipine besylate in each medium, was determined at different time intervals (0, 15 and 60 min) after filtering the content of each test tube by Whatman filter paper, the S(-)- amlodipine besylate content was determined spectrophotometrically at 239 nm.

### In vitro Dissolution Study of S(-)- amlodipine besylate

The formulation WMS 3 [Wet granulation, microcrystalline cellulose:starch blend (50:50)], showed promising results, Table 1, and was subjected to in vitro dissolution study in USP XXIV dissolution apparatus type II at  $37 \pm 0.5^\circ\text{C}$  and at 75 rpm, using 500 ml of dissolution media pH 1. 2. The dissolution profile was compared

with that of marketed preparation. The results recorded in Table 4.

### Content uniformity

Content uniformity of the optimized batches was also studied, using HPLC, Shimadzu (model:LC - 2010HT). The results noted in Table 4.

### Stability Studies

The selected formulation WMS 3 was studied for accelerated stability studies as per the ICH guidelines (11). The optical rotation of S(-)- amlodipine besylate in the formulation was measured using Polarimeter, Perkin Elmer (model: 341).

## RESULTS AND DISCUSSION

The studies revealed that the drug S(-)- amlodipine besylate has very poor flow property and a very good compressibility Carr's index (11.11) (Table 3). Microcrystalline cellulose: starch blend gave the satisfactory Carr's index (16), Hausner's ratio (1.180) and angle of repose ( $24^\circ$ ). The blend appeared to be the better alternative to lactose:starch blend, since it had better compressibility and flow property. The 5% concentration of starch paste gave optimized results, in terms of hardness and friability.

The direct compression S(-)- amlodipine besylate blend showed poor compressibility, flowability, hardness and content uniformity. The wet granulation technique using microcrystalline cellulose: starch blend showed promising results and was selected.

**Table 1: Formulation of S(-)- amlodipine besylate by wet granulation techniques**

Batch Parameters	WLS 1	WLS 2	WLS 3	WMS 1	WMS 2	WMS 3
Lactose:Starch	100:00	75:25	50:50	-	-	-
MCC:Starch	-	-	-	100:00	75:25	50:50
Starch Paste	5%	5%	5%	5%	5%	5%
Crosscarmellose Sodium (%w/w)	1%	1.5%	2.0%	-	-	-
Hardness (kg/cm <sup>2</sup> )	4.0	3.0	2.0	8.0	6.0	5.0
Friability (%w/w)	0.1	0.2	0.3	0.05	0.1	0.15
Disintegration (sec)	180	120	90	30	50	60

Each tablet contains 5 mg S(-)- amlodipine besylate, each tablet weighs 125 mg

WLS- Wet granulation using lactose:starch blend, WMS-Wet granulation using microcrystalline cellulose:starch blend.

**Table 2: Formulation of S(-)- amlodipine besylate by direct compression techniques**

Batch Parameters	DLS 1	DLS 2	DLS 3	DMS 1	DMS 2	DMS 3
Lactose:Starch (LS)	100:00	75:25	50:50	-	-	-
MCC:Starch (MS)	-	-	-	100:00	75:25	50:50
Crosscarmellose	1%	1.5%	2.0%	-	-	-
Sodium (%w/w)						
Hardness (kg/cm <sup>2</sup> )	2.0	1.4	1.0	3.0	2.2	1.6
Friability (%w/w)	1.5	2.0	2.5	0.9	1.8	2.2
Disintegration (sec)	160	90	75	20	42	56

Each tablet contains 5 mg S(-)- Amlodipine besylate, each tablet weighs 125 mg

DLS- Direct compression using lactose:starch blend, DMS- Direct compression using microcrystalline cellulose:starch blend

**Table 3: Effect of diluent on derived properties of S(-)- amlodipine besylate granules.**

Batch Parameters	Drug Without Diluents	WLS 1	WLS 2	WLS 3	WMS 1	WMS 2	WMS 3
Bulk density (g/ml)	0.555	0.460	0.372	0.339	0.421	0.404	0.382
Tap density (g/ml)	0.625	0.622	0.532	0.492	0.480	0.465	0.451
Carr's index	11.11	26	29	31	11	13	16
Hausner's ratio	1.125	1.352	1.430	1.322	1.140	1.150	1.180
Angle of repose (°)	>50	28	30	32	18	22	24

WLS- Wet granulation using lactose: starch blend, WMS- Wet granulation using microcrystalline cellulose:starch blend.

**Table 4: Content and dissolution profile of S(-)- amlodipine besylate tablet formulation and marketed preparation.**

Product	Content (%w/w)	Dissolution media	% Released 45 (min)
WMS 3	100.08	pH 1.2	99.89
Marketed Preparation	98.99	pH 1.2	91.56

WMS 3: Wet granulation microcrystalline cellulose:starch blend (50:50)

Experiments with solubility study of S(-)- amlodipine besylate in various physiological pH, revealed that S(-)- amlodipine besylate is soluble in pH 1.2. Hence pH 1.2 was the ideal dissolution media, to study in vitro release profile of S(-)- amlodipine besylate. The optimized batch of S(-)- amlodipine besylate tablet formulation WMS 3 was studied for the content uniformity and in vitro release profile in the above me-

dia. The results indicated improved dissolution profile of the formulated S(-)- amlodipine besylate tablet WMS 3 as compared with the available marketed preparations. The content uniformity was found to be NLT 85% and NMT 115%. The accelerated stability studies as per ICH guidelines revealed no change in optical rotation of S(-)- amlodipine besylate, NLT 24.0c (10% w/w solution in methanol).

### CONCLUSION

The formulation and dissolution profile of formulation WMS 3 was encouraging. The trial conducted with consecutive three batches revealed RSD below 2%, indicative of insignificant batch-to-batch variation. The formulation showed improved dissolution as compared to the marketed preparation. Thus the formulation of S-(-)- amlodipine besylate using microcrystalline cellulose:starch blend would be cost effective and dissolution media pH 1.2 would be the ideal media for conducting dissolution studies.

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