Online Available at www.thepharmaresearch.info

THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2010), 4-2; 253-259.
Published on- 15 Mar 2011

Original Article

ISSN 0975-8216

DESIGN, DEVELOPMENT AND CHARACTERISATION OF FIXED DOSE COMBINATION OF RAMIPRIL AND AMLODIPINE CAPSULES

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ABSTRACT

The main objective is to develop a stable Formulation of Ramipril and Amlodipine in fixed dose Combination throughout the designed Shelf life. The fixed dose combination is useful in reducing Hypertension, cardiac failure, particularly in diabetic patients. Ramipril acts by inhibiting Angiotensin converting enzyme and Amlodipine acts by blocking the calcium channels. The combination of the two classes of drugs produce Synergistic action and better management of hypertension both in geriatric patients and patients suffering from diabetes. The present work involves the development of the stable formulation using the compatible Excipients and exposing the samples to Accelerated stability conditions thus predicting the shelf life. Totally RACS-001,RACS-002,RACS-003,RACS-004,RACS-005 trial batches are prepared and evaluated for Bulk density, Tapped density, Weight variation, Disintegration time, and Content uniformity, Assay and Evaluation for Dissolution profile and found all the parameters are within the specifications.

Keywords: - Ramipril, Amlodipine, hypertension, Disintegration time, Dissolution profile.

INTRODUCTION

In more recent times capsule has been described a solid oral dosage form, which consists of a container, usually made of gelatin filled with a medicinal substance. The release of drugs from hard gelatin Capsules can be influenced by the formulation, it is important to consider the ways in which maximization and or consistency of drug release can be achieved. An important feature of formulation is to ensure that the capsule contains the correct, uniform dosage of the drug. The formulation will only exist in single component system if the drug completely and reproducibly fills the capsule volume. Small dose levels of drug require prior blending with inert diluents. Similarly large doses can be blended with a diluents if, by this

addition, a greater reproducibility of bulk volume can be achieved Glidants may also be needed to improve the powder flow and ensure reproducible volume. In order to ensure adequate bioavailability when formulating hard gelatin Capsules, it is necessary to consider various factors. They include Solubility, particle size, and wet ability of the drug together with the combination of Additives. To meet the therapeutic needs of Cardio Vascular patients with Hypertension, a rational fixed dose combination of Amlodipine and Ramipril is required. The main objective is to develop a stable Formulation of Ramipril and Amlodipine in fixed dose Combination throughout the designed Shelf life. The fixed dose combination is useful in reducing Hypertension, cardiac failure, particularly in diabetic patients. Ramipril acts by inhibiting Angiotensin converting enzyme and Amlodipine acts by blocking the calcium channels. The combination of the two classes of drugs produce Synergistic action and better management of hypertension both in geriatric patients and patients suffering from diabetes. The present work involves the development of the stable formulation using the compatible Excipients and exposing the samples to Accelerated stability conditions thus predicting the shelf life.

MATERIALS AND METHODS

Ramipril BP (micronized) is procured by Pfizer Pharmaceuticals Gujarat, Amlodipine Besilate BP is procured by novartis pvt. ltd. Gujarat, hydroxy propyl methyl cellulose (15cps) IP is procured by Torrent pharmaceuticals Gujarat, isopropyl alcohol IP, methylene chloride IP, starch 1500 lm grade, Tromethamine USP are procured by chemicals pvt. Ltd.

FORMULATION OF CAPSULES

Preparation of Ramipril granules:

STEP 1 SIFTING:

Sift specified quantity of Ramipril through # 12 meshes and collect separately in a clean doubled polythene lined bag and label.

STEP 2

Preparation of granulating solution:

1) Disperse specified quantity of HPMC 15cps in specified quantity of Methylene chloride in a clean SS vessel. .
2) To the above SS vessel add Isopropyl Alcohol and kept it for stirring for 5 minutes.

STEP 3 Granulation of Ramipril:

1) Transfer the above sifted Ramipril carefully in to the Planetary mixer.
2) Start the impeller at low speed.
3) Add the granulating Suspension of STEP 2 to the above material in Planetary Mixer under mixing at slow speed of the impeller. After adding 75% of the granulation suspension, stop further addition of the suspension and semi-dry the wet mass in a tray dryer at 40°C.
4) Transfer the Semi dried granules in to the above Planetary Mixer and continue granulation at the slow speed of the impeller till all the granulating Suspension is exhausted.

STEP 4 Drying:

5) Dry the above-granulated wet mass in a tray dryer at 40°C till the Loss on drying of the drug granules at 60°C is below 1.0%. W/w.

LOD at 60°C = 0.93% w/w

STEP 5 Sifting:

6) Sift the drug granules through # 40 meshes passed and collect in a double polythene lined container. Send the material for the determination of assay.

STEP 6 Granulated Ramipril of step 5:

After getting analytical report of step 5, calculate the quantity of the granulated

Ramipril required to be added in to the batch as per the fallowing formula.

Procedure:

- Pass Amlodipine Besilate and starch 1500 through #40 mesh
- Sift the above mixture with Ramipril granules and #100 meshes pass Tromethamine in a geometric dilution technique.
- Blend the above mixture for 30 minutes in a 1 liter blender.

Geometric Dilution

The geometric dilution technique is used for potent drugs

- Take equal quantity of drug and excipient and pass through the required mesh.
- Take the above sifted material and add same quantity of excipient and pass through the same mesh.
- Again take the above sifted material and add same amount of excipient and pass through the same mesh.

Note:

Starch 1500 LM grade to be dried at 90°C TO 100°c in a tray dryer to bring down LOD of the material to NMT 3% at 105°C using an IR moisture Analyzer.

TABLE- 1 FORMULATION CHART

Ramipril BP Granules		
S.NO	**INGREDIENTS**	**MG/CAP**
1	Ramipril BP	5.309
2	HPMC 15 CPS	0.5309
3	ISOPROPYL ALCOHOL	5.309
4	METHYLENE CHLORIDE	0.5309
Ramipril and Amlodipine Formulation		
S.No	**INGREDIENTS**	**MG I CAPSULE**
1.	Ramipril granules	5.84
2.	Amlodipine Besilate	6.9
3.	Starch 1500 LM grade	126.76
4.	Tromethamine USP	0.5
Variables		
S.No	**Batch**	**Scale Up (Times)**
1.	Batch RACS-001	1
2.	Batch RACS-002	2
3.	Batch RACS-003	10
4.	Batch RACS-004	20
5.	Batch RACS-005	25

RESULTS AND DISCUSSION

B.No: RACS-001

Results: The uniformity of content is found to be satisfactory at 40min of blending. The capsules are filled at 40 min and given for complete analysis. The content uniformity was found to be satisfactory at 40 minutes of blending time and the results are found in the table. The assay, dissolution at 45 minutes is found to be satisfactory. Exposure studies of

the above trial had been performed by exposing the samples in Aluminum pouches for 30 days and the analyzing the same for the assay and the dissolution and impurities. The Ramipril was found to be degrading at 60°C and the remaining parameters were found to be within the limits.

B.No: RACS-002

When increasing the batch size to 10,000 capsules has performed the same trial and the samples at the blend stage are performed for uniformity at different intervals such as 30' 45' 60' 90' 120 Minutes respectively. The RSD was found to be 3.305 at 90' and 2.056 at 120' respectively.

B.No: RAC5-003

The samples were collected at the blending stage at different intervals as 30' 40' 45' and are tested for their uniformity of content. The results are found to be satisfactory at 45' and hence the same blending time has been followed for the further batches. The complete analysis report is given in Table No: 3 and all the results are found to be satisfactory.

B.No: RAC5-004

The samples were collected at the blending stage at different intervals as 30' 40' 45' and are tested for their uniformity of content. The results are found to be satisfactory at 45'

B.No: RAC5-005

The samples were collected at the blending stage at different intervals as 30' 40' 45' and are tested for their uniformity of content. The results are found to be satisfactory at 45'

TABLE- 2 OBSERVED PARAMETERS

S.NO	PARAMETERS	Batch RACS-001	Batch RACS-002	Batch RACS-003	Batch RACS-004
1	Disintegration time	3.18 min	2.0min.	2.1min.	2.5min.
2	PH of 1 % solution	5.34	5.4	5.38	5.31
3	Length of the Capsules	14.6mm, 14.2mm, 14.79mm, 14.61mm.	14.6mm, 14.31mm, 14.21mm, 14.42mm	14.72mm, 14.51mm, 14.44mm, 14.52mm, 14.50mm.	14.72mm, 14.51mm, 14.29mm, 14.69mm, 14.81mm 14.32mm
4	Individual weight of the Capsules	179.0mg, 178.9mg, 182.6mg, 180mg, 184.3mg 182.1mg.	179.0mm, 178.2mm, 180mm, 182.6mm, 181.2mm 181.9mm.	181.0mm, 184.2mm, 180.6mm, 179.2mm, 176.2mm 177.4mm.	180Amm, 179.2mm, 178.9mm, 182.2mm, 185.9mm, 183.2mm.
5	Bulk density (Un-Tapped)	0.545g/mL	0.588 g/ml	0.588g/ml	0.532g/ml
	Tapped density	0.789 g/mL	0.857 g/ml	0.833g/ml	0.839g/m1

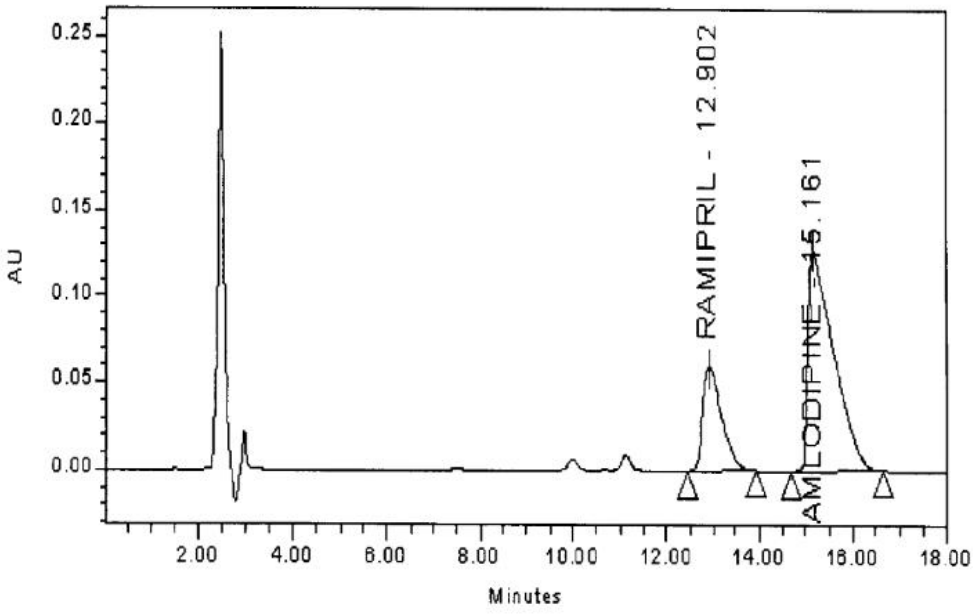
TABLE-3 RESULTS

Batch		Batch RACS-001	Batch RACS-002	Batch RACS-003	Batch RACS-004	Batch RACS-005
Avg. weight of the capsule		181.5 mg	180.6	180.6	180.7	180.4
Avg. net content		141.0 mg	141.0	141.0	142.6	142.0
Water		6%	6%	6%	4.8%	5.4%
Dissolution amlodipine		92.76%	85.76%	111.4%	92.56%	87.13%
Dissolution Ramipril		108.416%	99.174%	138.4%	99.33%	99.133%
Content of amlodipine (Assay)		4.82	4.74	4.74	4.75	4.73
Content of Ramipril (Assay)		5.42	5.47	5.37	4.99	5.04
DT Min		3.8	3.8	3.6	4.0	4.2
Content Uniformity at 45 mnts	amlodipine	3.75	2.3	2.1	2.35	1.32
	Ramipril	3.212	1.46	1.42	2.61	2.61

Table- 4: List of innovator's / competitors' product

S. No	Brand Name	Manufacture	Country	Strength	Dosage form
01	CARDACE	HOESCHST AROIN	U.S.A	5.0 MG	CAPSULES
02	AMLOGUARD	PFIZER	U.S.A	5.0 MG	TABLET

Fig-1: TYPICAL CHROMATOGRAM:



CONCLUSION

In the present work on attempt made to formulate and develop fixed dose combination product of Ramipril and Amlodipine besilate belonging to two different classes of Anti-hypertensive drugs. Ramipril acts by inhibiting Angiotensin Converting Enzyme inhibitor while Amlodipine is a long acting calcium channel blocker. The combination of these two classes of drugs produces synergistic action and thus betters management of hypertension particularly in geriatric patients. These two drugs are combined and presented in the form of hard gelatin capsules. Ramipril being a molecule sensitive to moisture, air and heat it is coated using a water soluble polymer i.e., Hydroxy propyl methyl cellulose 15 cps which renders the molecule to be stable. The coating rapidly dissolves in the GI fluids and releases the drug immediately to show its therapeutic action. These is followed by direct blending of the other drug and the diluent and fill the remaining blend in #4 size capsules with a fill weight of 140mg + 5%. Use of the combination drugs: Better management of hypertension in geriatric patients, Synergistic action. Totally RACS-001, RACS-002, RACS-003, RACS-004, RACS-005 trial batches are prepared and evaluated for Bulk density, Tapped density, Weight variation, Disintegration time, and Content uniformity, Assay and Evaluation for Dissolution profile and found all the parameters are within the specifications. The Trial Batches RACS-003, RACS-004 and RACS-005 are optimized and kept for stability studies for 6weeks, Evaluated for Dissolution, Impurities and Moisture content and it is found there is no significant change in the parameters after the stability studies.

ACKNOWLEDGEMENT

Authors are thankful to Prof. (Dr.) B. Jayakar, principal Vinayaka Missions College of pharmacy, Salem, Tamilnadu and providing all the facilities for this research Project.

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