JOURNAL OF DRUG DELIVERY RESEARCH
ISSN 2319-1074

RESEARCH ARTICLE

FORMULATION EVALUATION AND DEVELOPMENT OF SUSTAINED RELEASE TABLETS OF INDAPAMIDE & IMMEDIATE RELEASE BLEND OF RAMIPRIL IN CAPSULES

R.Margret Chandira*, Thakor Pranavkumar P, M.V.Kumudhavalli,Debjit Bhowmik, B. Jayakar

Department of pharmaceutical sciences
Vinayaka missions college of Pharmacy
Vinayaka mission University
Salem,Tamilnadu

ABSTRACT

The present investigation relates the development of a Capsule containing Sustained Release Tablet of Indapamide & Immediate Release blend of Ramipril as a combinational therapy against Antihypertension. The combination of Ramipril-Indapamide is well tolerated and the efficacy is maintained over 1-year period. The combination of Ramipril-Indapamide exhibits an improved safety profile, whereby hyperkalemia associated with Ramipril is attenuated by co administration of Indapamide, which is associated with Hypokalemia. Matrix tablet of Indapamide formulated using Hydrophilic Polymer HPMC K4M ,HPMC K15M,HPMC K100M & Combination of these. For Indapamide SR tablets wet granulation was method of choice. Optimization was done and it was found that release profile was found to be best with single polymer i.e. HPMC K4M and granulation with PVPK30 in IPA solution gave the desired binding. Film coating of Opadry AWB-2 White aqueos coating 3%w/w was done on Indapamide tablets as to avoid any interaction with ramipril blends. Special care was taken for Ramipril processing in low humidity condition and geometric mixing is applied to avoid content uniformity and segregation. Stabilizers like MgO & Sodium bicarbonate were added to provide an alkaline atmosphere to improve the stability of drug.The % drug content of formulation for Indapamide F-11 were 101.7 & for Ramipril Batch no. 5 % drug content was found to be 102.5% at 45 min.The stability study showed that there is no significant changes in In-vitro release ,Assay at accelerated condition of temperature for 3 months.

Keywords - Indapamide,Ramipril,Antihypertensive therapy,Matrix tablet.

INTRODUCTION

Scenario of pharmaceutical drug delivery is rapidly changing whereby conventional pharmaceutical dosage forms are being replaced by new drug delivery systems. These new drug delivery systems are having edge over conventional ones in terms of many biopharmaceutical parameters. of these, technologies sustained release formulations have maximum mileage and research in this field has been extremely fertile and has produced many discoveries having good commercial advantage and with better physician – patient satisfaction. The primary objective of sustained-release drug delivery system is to ensure safety, efficacy, reduced dose and frequency results in improved patient compliance.Aim of the present study is to Formulation development & evaluation of Sustained Release tablets of Indapamide & Immediate release blend of Ramipril in a capsule as a combinational Antihypertensive therapy as a stable,safe & effective formulation. Drug Combinational therapy offer improved efficacy and response, as combination

of Ramipril with other diuretic provides synergistic antihypertensive effect in controlling blood pressure Ramipril-diuretic combination. Among all diuretics, Indapamide has low dosage, high solubility, and short half life to treat hypertension. So, combination of Ramipril and Indapamide provide synergistic effects in treatment of mild to moderate hypertension**.**

Tablet manufacturing:

manufacturing of indapamide SR tablets:

Wet Granulation Process

The corresponding amounts of drug (Indapamide), Lactose Monohydrate and

MCC pH 102, HPMC K4M were accurately weighed

The powders were screened using screen #40.

The screened powder was transferred into the Rapid Mixture Granulator and mixed for 5 minutes.

The corresponding amount of PVPK30 accurately weighed, dispersed in to the IPA

and stirred till the clear colloidal solution obtained.

The powder mixture which was transferred to the Rapid Mixture Granulator granulated with binder solution.

Binder added for 3 min at Impeller speed of 150 RPM keeping chopper off.

Kneading was done for another 2 min at impeller speed of 150 RPM and Chopper speed of 1500 RPM.

Wet mass was dried in a tray dryer at temp of 50 -60°c till the LOD of 2 % achieved

The dried mass was passed through a #20 sieve and the resulting granules were packed in the polybag.

The dried granules and the corresponding amount of Aerosil® is accurately weighed and then mixed in the polybag or cage blender for 3 minutes.

Corresponding amount of Magnesium stearate was then mixed with the blend in the polybag or Cage Blender for 2 minutes.

The mixture was compressed into tablets using an instrumented tablet press with

6mm punches for 100mg weight at 7-8kp hardness and tablets were collected during compression for in-process testing (weight, friability and hardness).

(A) The drug (Ramipril) was screened using screen #40, and Pregelatinised starch accurately weighed & screened using screen #40.The screened powder was transferred into the polybag in 1:10 ratio and mixed for 3 minutes.Pass it every time through 40#,further mix for 2 min.Geometric mixing with remaining Pregelatinised starch is done in same proportion.

MCC 102 pass through 40#,mix well for 3 min with A & pass it through 40#.

Sodium bi carbonate and magnesium oxide, used as alkanizer are passed through screen #40 was transferred into the cage blender and mixed for 5 minutes.

Sodium stearyl fumrate as lubricant is accurately weighed & screen #60 is then mixed in the polybag or cage blender for 3 minutes with the blend prepared.

The mixture was filled into

capsule of size one with Indapamide SR tablet.

Formula for Batches of Indapamide SR Tablet:

TABLE: 1 Indapamide batch record IND 1 to 6

Batch No.	IND-1	IND-2	IND-3	IND-4	IND-5	IND-6
Ingredients	**mg/tablet**					
Indapamide	1.53	1.53	1.53	1.53	1.53	1.53
Lactose Fast Flow	-	-	-	-	48.30	-
Lactose Monohydrate	-	48.64	48.26	45.06	-	38.84
PVPK30	3.20	3.44	3.44	3.44	3.44	3.44
HPMC k 15M	32.00	25.22	21.26	24.80	25.22	-
HPMC k4M	-	-	-	4.80	-	35.50
HPMC k100M	-	-	3.84	-	-	-
IPA	q.s.	q.s.	q.s.	q.s.	-	q.s.
Aerosil	0.2	0.2	0.2	0.2	0.4	0.2
Mg. Stearate	1	1	1	1	0.8	0.8
Tablet Weight	**80mg**					

TABLE: 2 Indapamide Batch Record IND 7 To 12						
Batch no.	**IND 7**	**IND 8**	**IND 9**	**IND 10**	**IND 11**	**IND 12**
Ingredients	**%**					
Indapamide	1.53	1.53	1.53	1.53	1.53	1.53
MCC 102	-	-	-	8.00	9.60	9.60
Lactose Monohydrate	38.28	29.50	33.50	25.90	24.30	23.90
PVPK30	4.00	4.00	4.00	3.60	3.60	4.00
HPMCk-4M	35.50	44.00	40.00	40.00	40.00	40.00
IPA	**q.s.**					
Aerosil	0.2	0.2	0.2	0.2	0.2	0.2
Magnesium Stearate	0.8	0.8	0.8	0.8	0.8	0.8
Tablet Weight	**80mg**					

Film Coating For Indapamide SR Tablets:

TABLE: 3 Ingredients used in Film coating		
Sr.No.	**Ingredients**	**Quantity (%w/w)**
1.	Opadry AWB-2 White	10%
2.	Millipore water	90%

TABLE: 4 Optimised Parameters for Film Coating for Indapamide SR Tablets			
Conditions	**Pre-heating**	**Coating**	**Drying**
Inlet air temperature (°C)	55-60	60-65	50
Product temperature (°C)	55-60	50-55	55-60
Outlet air temperature (°C)	35-60	55-60	50-55
Spray rate (ml/min)	-	1-2	-
Atomizing air pressure (psi)	-	20	
Pan speed (rpm)	35-37	35-37	35-37

MANUFACTURING OF RAMIPRIL IR BLEND:

Formula for Trial Batches For Ramipril IR granules:

TABLE:5 Ramipril IR 5mg blend Batches With Different Approaches

Batch no.	**Ramp-1**	**Ramp-2**	**Ramp-3**	**Ramp-4**	**Ramp-5**	**Ramp-6**
Ingredients	**%mg/cap**					
Ramipril	5.27	5.27	5.27	5.27	5.27	5.27
Starch Preg.	109.20	109.20	40.00	98.5	104.00	104.00
MCC Ph 102	88.20	83.20	-	-	88.25	88.25
Sodium Stearyl Fumrate	2.10	2.10	2.10	2.10	2.10	2.10

Lactose unhydrous	-	-	-	100.0		
Na_2 HCO_3	5.25	5.25	5.25	-	5.25	5.25
Meglumin	-	5.25	-	5.25	-	-
Compactrol	-	-	157.5	-	-	-
Magnesium oxide	-	-	-	-	5.25	5.25
Total	**210mg**					

Chemical Characterization of Ramipril Innovator Capsule:

TABLE 6 RAMIPRIL INNOVATOR CAPSULE DISSOLUTION

Dissolution Media (500ml Media, at 75rpm)	**Number of Units Used 6**	**Percentage of Drug Dissolved in Minutes**				
		5	**10**	**15**	**30**	**45**
0.1 N HCL	**Mean**	100.1	105.4	105.7	106.3	107.3
	± **SD**	3.6	2.8	2.8	3.3	3.1
	± **RSD**	3.6	2.6	2.7	3.1	2.9

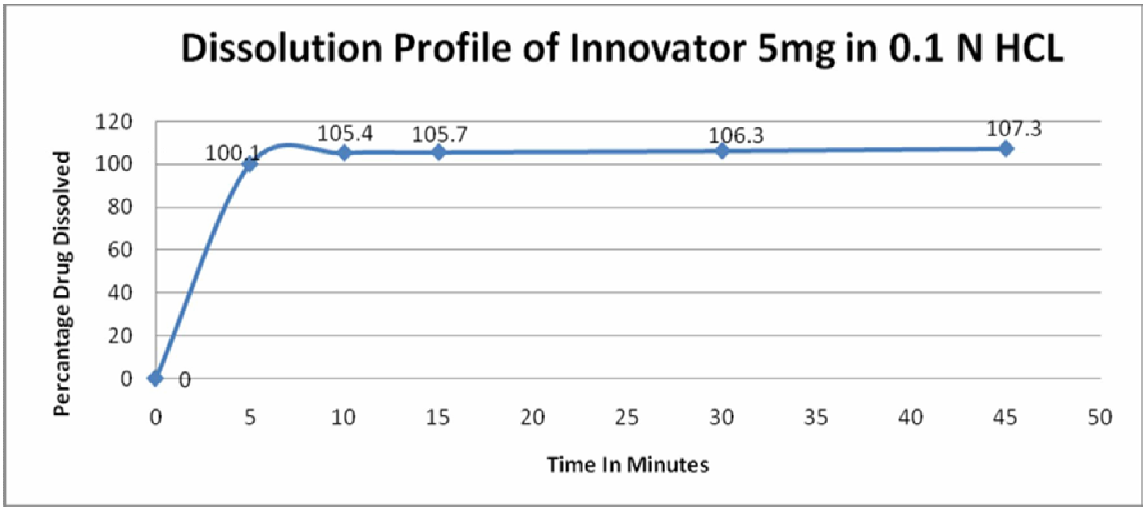

FIGURE: 1 Dissolution Profile Of Innovator Capsule(Altace) Of Ramipril 5 Mg In 0.1N Hcl

RAMIPRIL IR BLEND FORMULATION DEVELOPMENT

Table : 7 Ramipril Blend Analysis Data Batches Ramp.1-5

Batch No.	Ramp 1	Ramp 2	Ramp 3	Ramp 4	Ramp 5	Ramp 6
Bulk Density	0.44g/ml	0.47g/ml	0.43g/ml	0.49g/ml	0.45g/ml	0.46g/ml
Tapped Density	0.65g/ml	0.62g/ml	0.59g/ml	0.89g/ml	0.58g/ml	0.60g/ml
Hausner Ratio	1.47	1.31	1.37	1.81	1.28	1.30
Angle of Repose	41°.09'	32°.35'	37°78'	51°36'	28°20’	30°10’

Table 8 : Ramipril Blend Particle Size Distribution Data Batches Ramp.1-5					
Analysis	**Particle Size Distribution (PSD)**				
Batch No.	**Ramp. 01**	**Ramp. 02**	**Ramp. 03**	**Ramp. 04**	**Ramp. 05**
Retained on #20	**Nil**	**Nil**	**0.03%**	**0.28%**	**0.32%**
#20 / #40	**1.23%**	**1.35%**	**4.04%**	**3.20%**	**2.65%**
#40 / #60	**22.83%**	**19.72%**	**18.56%**	**16.78%**	**17.32%**
Passed Through #60	**75.53%**	**76.38%**	**77.32%**	**81.60%**	**78.93%**

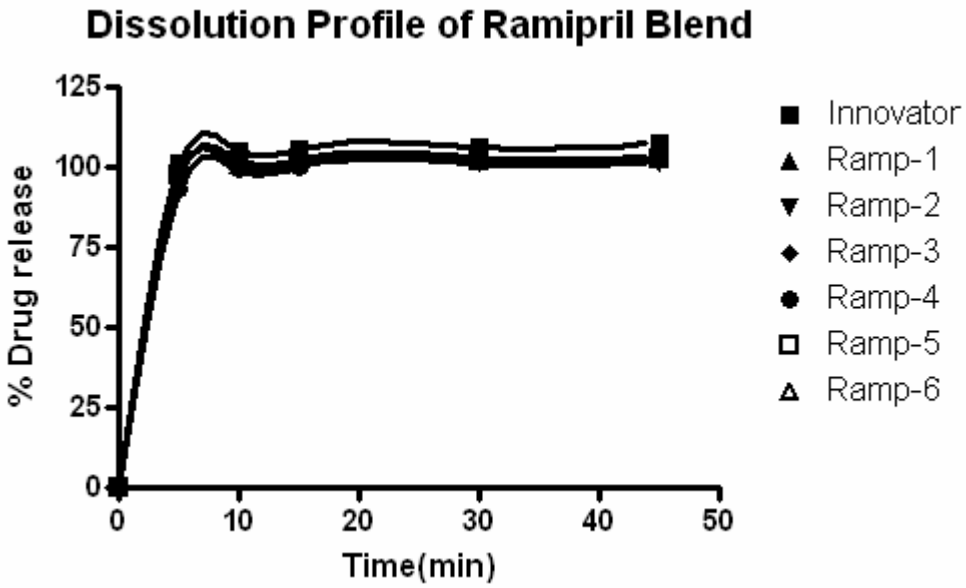

FIGURE-1 Dissolution profile Ramipril blend

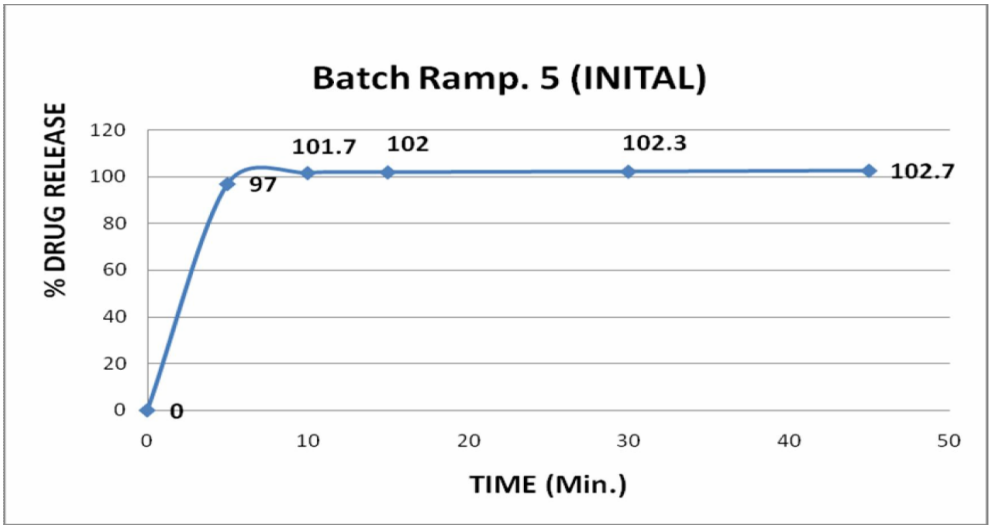

Figure-2 **Dissolution Profile of Ramipril Blend Batch Ramp.5**

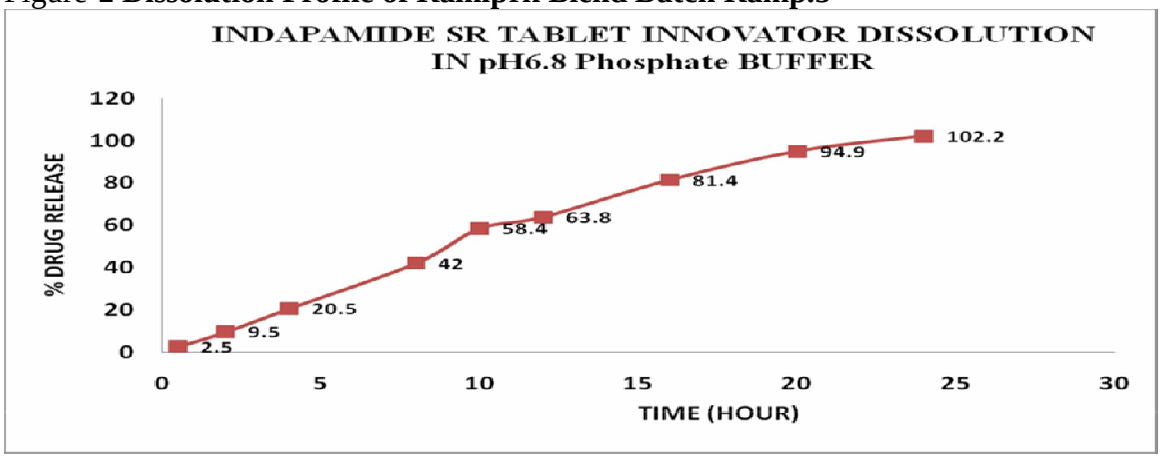

Figure-3 Dissolution Profile Of Innovator Tablet Of Indapamide 1.5 Mg In Official Media

Conclusion:

The research work was aimed with formulation development of immediate release blend of Ramipril and sustained release tablet of Indapamide in a capsule as combinational antihypertensive therapy. Ramipril is an ACE inhibitor and Indapamide is a diuretic used in combination for treatment of chronic hypertension. Thus, it was concluded that the optimized formula (Batch IND-11) for Indapamide SR tablets and (Batch Ramp-5) for Ramipril IR blend are stable under accelerated conditions of temperature and humidity. The formulations were found to be comparable with innovator (reference) formulations, with respect to physicochemical parameters having better in-vitro release profiles.The final formulation was filled in a capsule of size one consisting of Ramipril IR blend 5mg and Indapamide SR tablet of 1.5mg to be packed in alu strip of 10 capsules per strip. It is used in case of chronic hypertension, once daily giving 24 hours maintenance therapy

for hypertension.

REFERENCES

1. P.D. Nakhat, P. G. Yeole, U. C. Galgatte, I.B. Babla, in, "Ind. J. Pharm. Sci. 2006,68(2), Pg.No.185-189.
2. Becker C, Dressman JB, Amidon GL, Junginger HE "Biowaiver monographs for IR solid oral dosage forms: Isoniazid" J Pharm Sci.2007 Mar; 96(3):522-31
3. Dumont ML, Berry MR, Nickerson B "Probability of passing dissolution acceptance criteria for an immediate release tablets" J Pharm Biomed Anal. 2007 Feb 3
4. Qureshi SA, Shabnam J "Applications of a new device (spindle) for improved characterization of drug release (dissolution) of pharmaceutical products." Eur J Pharm Sci. 2003 Jul; 19(4):291-7
5. Yu LX, Wang JT, Hussain AS "Evaluation of USP apparatus 3 for dissolution testing of immediate release products" AAPS PharmSci. 2002; 4(1):E1
6. Shah VP, Gurbarg M, Noory an "Influence of higher rates of agitation on release patterns of immediate-release drug products" J Pharm Sci.1992 Jun; 81(6):500-3
7. Yong CS, Jung JH, Rhee JD, Kim CK, Choi HG, Physicochemical Characterization and Evaluation of Buccal Adhesive Tablets Containing Omeprazole, Drug Development and Industrial Pharmacy. 2001; 27(5): 447 – 455.