Journal of Pharma Research
Available online through
www.jprinfo.com

Research Article
ISSN: 2319-5622

Design, Fabrication and Invitro Evaluation of Irbesartan and Simvastatin Bilayered tablets

Naikar Nuzhathullah*, Raju. Manda., Dr. R. Suthakaran
Teegala Ram Reddy College of Pharmacy, Meerpet Hyderabad– 500097, Telangana (State). India.

Received on: 15-10-2014; Revised and Accepted on: 25-10-2014

ABSTRACT

Bilayered tablets consists of two different granulations that are compressed to form a single tablet composed of two layers and usually each layer is of different colour to produce a distinctive looking tablet. In this study, an attempt has been mad Irbesartan to prepare bilayered tablets of Irbesartan and Simvastatin. Immediate release layer of Irbesartan and Simvastatin as Sustained release. Various formulations of Simvastatin layer were prepared using various combinations of excipients. Immediate release layer of Irbesartan was prepared by wet granulation method. Sustained release layer of Simvastatin was prepared by Direct Compression method using CARBOPOL, EUDRAGIT and HPMC as release retardants as well as carriers. Drug polymer compatibility was performed by FTIR. Tablets were evaluated for their physicochemical properties, in vitro drug release and stability studies. The evaluation parameters were found uniform and reproducible. The tablets produced met with the I.P requirement regarding drug content uniformity, hardness, disintegration and friability. All the formulations produced were studied for their drug in dissolution media of 0.1N HCl and 6.8 pH phosphate buffer. Formulation ***(FT11)*** *containing HPMC and CARBOPOL (1:1) was found to be the best formulation it extend the release up to 12 hrs.*

KEYWORDS: *Bilayered tablets; Irbesartan; Simvastatin; Angiotensin; In vitro drug release; FTIR.*

INTRODUCTION

Irbesartan is commonly used as Antihypertensive agent, MOA is it antagonizes Angiotensin2 by blocking AT1 receptor. Angiotensin II is the primary vasoactive hormone in the renin-angiotensin system. Its effect includes vasoconstriction and the stimulation of aldosterone secretion by the adrenal cortex. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking in a non competitive manner the binding of angiotensin II to the AT1receptor found in many tissues. Irbesartan has no agonist activity at the AT1 receptor. AT2receptors have been found in many tissues, but to date they have not been associated with cardiovascular homeostasis. Irbesartan has essentially no affinity for the AT2 receptors. Irbesartan does not inhibit angiotensin converting enzyme, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect renin or other hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostasis. It is soluble in organic solvents. Absorbance is determined at 234 nm. Protein binding in plasma is 96%. Half life is 11-15 hrs. our aim is to develop an immediate release formulation of irbesatan. Irbesartan layer is prepared by using wet granulation technique, the drug releases within one hour. Simvastatin is used for treatment of dyslipidemia & prevention of cardiovascular diseases. It acts by inhibiting 3hydroxy 3 methyl glutaryl co.A & there by inhibiting endogenous production of cholesterol. All statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway, the metabolic pathway responsible for the endogenous production of cholesterol. Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration [8]. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration.

MATERIALS AND EQUIPMENTS

Table No. 1: Materials and Equipments

S. No.	Materials	Category	Suppliers
1	Irbesartan	Anti hypertensive drug	AurobindoPharma,Hyderabad
2	Simvastatin	Antihyperlipidemicdrug	AurobindoPharma,Hyderabad
3	HPMC 15cps	Polymer	SDFCL Mumbai
4	Eudragit RL100	Polymer	Essel chem Mumbai
5	CrossCarmelloseSodium	Super dissintegrant	Essel chem Mumbai
6	Magnesium stearate	Lubricant & glidant	SDFCL Mumbai
7	PVPK30	Binder	NRchemicalsMumbai
8	Isopropanol	Solvent for PVPK30	NRchemicalsMumbai
9	Talc	Lubricant & glidant	SDFCL Mumbai
10	Fe_2O (colour)	Colourant	SDFCL Mumbai
11	MicroCrystallineCellulose	Diluent	Essel chem.. Mumbai
12	Carbopol 940	Polymer	NRchemicalsMumbai
13	Lactose	Diluent	SDFCL Mumbai

***Corresponding author:**
Naikar Nuzhathullah
Department of Pharmaceutics,
Teegala Ram Reddy College of Pharmacy, Meerpet -500097,
Telangana,(State) India. Mobile Number: 8985754211.
**E-Mail: nuzzu.916@gmail.com.*

Pre-formulation Studies:

Preformulation activities range from supporting discoveries identification of new active agents to characterizing physical properties necessary for the design of dosage form. Clinical information provides during Preformulation can enhance the rapid

and successful introduction of new therapeutics entities for humans. Preformulating testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form [6].

Formulation and Evaluation Methods:

Formulation of Tablets (Wet granulation method of Irbesartan and Dry granulation mothod of simvastatin). Evaluation of Tablets Properties of Tablets – Appearance, Size and Thickness, Hardness, Friability, Weight variation, Content uniformity, *In-vitro* Drug Release Studies , Kinetics of *In-vitro* Drug Release (Zero order, First order, Higuchi and Korsmeyer Peppas) and Stability Studies [3].

Table No. 2: Composition of Irbesartan layer

Formulation code (mg)	FI 1	FI 2	FI 3	FI 4
Irbesartan	150	150	150	150
Cross Carmellose Sodium	5	10	15	20
Micro Crystalline cellulose	52.5	47.5	42.5	37.5
Lactose	15	15	15	15
PVP K 30	24	24	24	24
Iso propyl alcohol	Qs	Qs	Qs	Qs
Magnesium stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Colouring agent (Fe_2o)	0 .50	0.50	0.50	0.50
Total weight (250 mg)	250	250	250	250

Take 150mg of Irbesartan to it add required quantity of Cross Carmellose Sodium, Lactose, MCC (pH101) according to formulations as mentioned in table pass them through sieveno.22 and mix it well. Prepare the binder by taking 24mg of pvpK30 in Q.S of Isopropanol, mix well, add 0.5mg of Fe_2O (colourant) stir it well. Now add drop by drop binder to mixture until it forms wetmass note the volume of binder. Now make them granules by passing it through sieveno.225. Dry the granules in oven at 60°c for 30min.Now sieve the dried granules by passing it through sieveno.22 and now add required quantity of Talc, Magnesium stearate which is passed through sieveno.44.Mix it well and store it in suitable container.

Table No. 3: Composition of Simvastatin layer

Formulation Code	Simvastatin (mg)	HPMC 15CPS (mg)	Eudragit RL100 (mg)	Carbopol 940 (mg)	MCC (pH101) (mg)	Magnesium Stearate (mg)	Talc (mg)	Total Weight (mg)
FS 1	40	20	_	_	178	6	6	250
FS 2	40	_	20	_	178	6	6	250
FS 3	40	_	_	20	178	6	6	250
FS 4	40	40	_	_	158	6	6	250
FS 5	40	_	40	_	158	6	6	250
FS 6	40	_	_	40	158	6	6	250
FS 7	40	60	_	_	138	6	6	250
FS 8	40	_	60	_	138	6	6	250
FS 9	40	_	_	60	138	6	6	250
FS 10	40	_	30	30	138	6	6	250
FS 11	40	30	_	30	138	6	6	250
FS 12	40	30	30	_	138	6	6	250

Composition of Simvastatin layer:

Weigh 40mg of simvastatin and pass it through sieveno.22.Take required quantity of excepients (polymers, MCC) according to each formulation as mentioned in table and pass them through sieveno.44 and mix them. Now add the above excipients powder to the powdered simvastatin triturate it well. Take required quantity of Talc and Magnesium stearate pass them through sieveno. Add them to triturated powder (drug+polymer+MCC). Mix it well and store it in suitable container [5].

Compression:

Pour required quantity (different formulations) of Irbesartan granules in round flat faced punch in the die cavity of tablet press using spatula, Irbesartan layer was pre-compressed to produce uniform layer. Now pour 220mg of simvastatin powder (different formulations) in the same cavity having uniform Irbesartan layer by using spatula, finally compressed with 9.5mm round flat punch. To obtain a tablet of optimum hardness and thickness. Bilayered tablets are formed collect them and store in suitable containers [3].

RESULTS AND DISCUSSION

Spectroscopic Studies:

UV Spectroscopy - Determination of λmax and Preparation of Calibration Curve of Simvastatin by using water, 0.1N HCl, Phosphate buffer pH 6.8, shows λmax at 247 nm, λmax of Irbesartan is determined by using water, 0.1N HCl shows λmax at 234 nm.

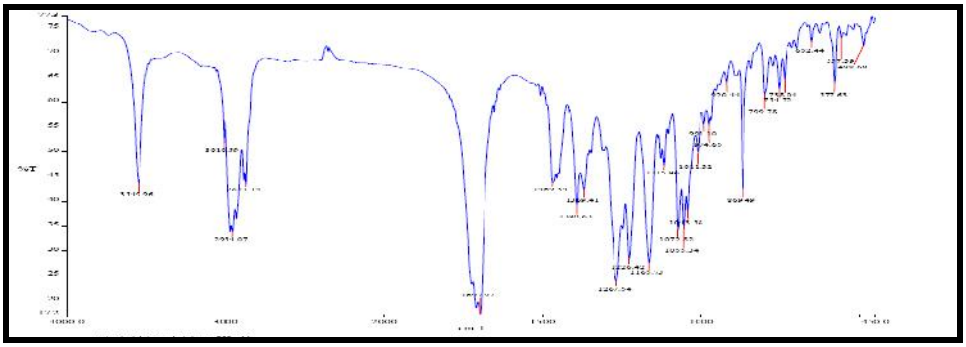

Fig. 1: FTIR spectrum of Simvastatin

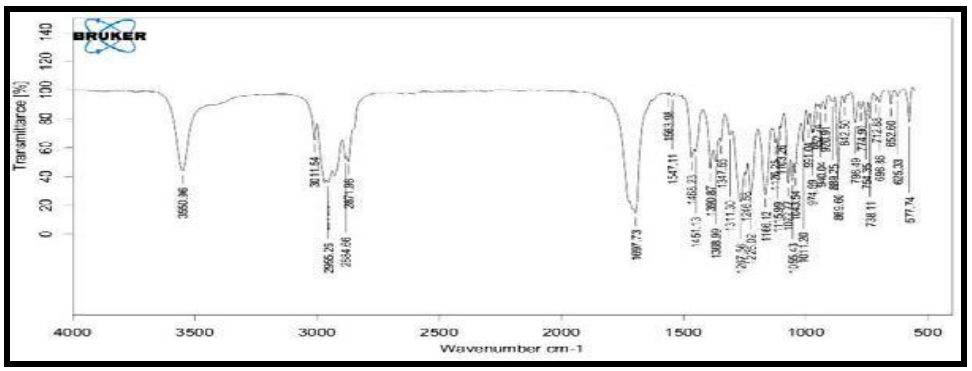

Fig. 2: FT-IR of Simvastatin+Carbopol+Eudragid+HPMC Compatability studies

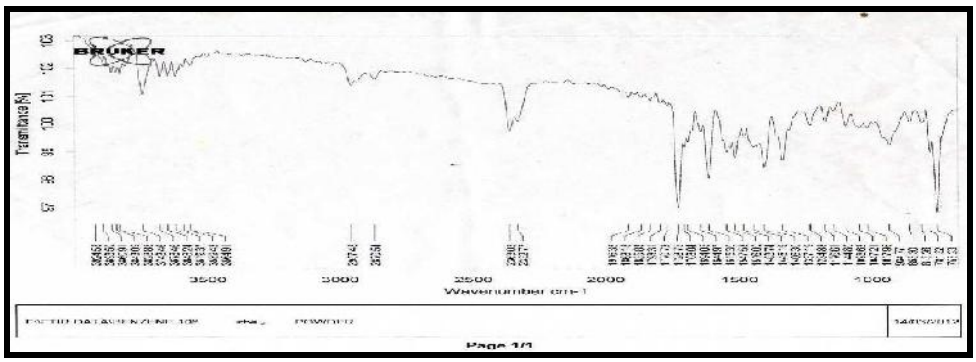

Fig. 3: FTIR spectrum of Irbesartan

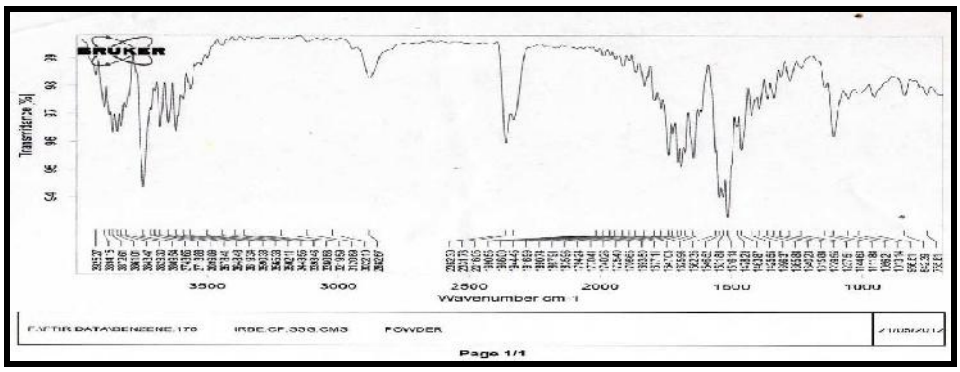

Fig. 4: FT-IR of Irbesartan+PVPK30+MCC+CCS Compatability studies

Table No. 4: Evaluation of pre-formulation parameters of irbesartan layer blend

Product code	Angle Of repose(°)	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index(%)	Hausner's ratio
FI 1	27.64±0.10	0.60±0.08	0.68±0.13	12.09±1.14	1.13±0.17
FI 2	29.00±0.85	0.59±0.03	0.68±0.06	13.74±1.17	1.14±0.32
FI 3	28.77±0.3	0.60±0.05	0.71±0.07	14.65±0.37	1.17±0.08
FI 4	26.11±0.71	0.63±0.11	0.70±0.04	11.46±1.15	1.12±0.11

All the values are expressed as a mean ± SD., n = 3

Table No. 5: Evaluation of pre-formulation parameters of simvastatin layer blend

Product code	Angle of repose(°)	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index (%)	Hausner's ratio
FS 1	25.46±0.41	0.61±0.09	0.74±0.12	16.71±1.21	1.21±0.71
FS 2	27.76±0.27	0.59±0.07	0.65±0.09	13.69±1.13	1.13±0.68
FS 3	23.3±0.93	0.63±0.13	0.72±0.17	14.60±0.45	1.14±0.72
FS 4	30.86±0.72	0.60±0.17	0.68±0.11	13.91±1.01	1.12±0.92
FS 5	26.0±1.12	0.62±0.21	0.70±0.14	14.25±0.51	1.13±0.58
FS 6	24.03±1.02	0.63±0.12	0.70±0.07	12.81±1.34	1.12±0.46
FS 7	24.33±0.66	0.60±0.08	0.71±0.03	14.11±0.72	1.17±0.71
FS 8	27.33±0.34	0.59±0.19	0.70±0.09	13.23±0.36	1.18±0.23

FS 9	30.46±0.21	0.57±0.07	0.66±0.04	13.79±1.02	1.14±0.07
FS 10	23.33±1.32	0.60±0.03	0.73±0.01	19.22±0.31	1.20±0.14
FS 11	22.23±0.72	0.57±0.09	0.64±0.05	12.52±0.72	1.12±0.03
FS 12	24.66±0.34	0.65±0.11	0.73±0.08	13.03±1.02	1.12±0.03

All the values are expressed as a mean ± SD., n = 3

Table No. 6: physical evaluation of bilayered tablets

F.code	Uniformity of Thickness (n=3) (mm)	Hardness (n=3) (kg/cm²)	Friability % (n=10)	Uniformity of weight (n=20) (mg)	Drug Content (n=3) (mg)
FT 1	4.1±0.2	4.76±0.12	0.39±0.01	498.9±0.1	93.63±0.07
FT 2	4.20±0.1	4.36±0.36	0.23±0.16	501±0.1	94.84±0.03
FT 3	4.08±0.22	4.53±0.14	0.28±0.11	498.4±0.2	91.45±0.12
FT 4	3.98±0.31	4.9±0.08	0.27±0.12	499.3±0.5	92.53±0.14
FT 5	3.96±0.35	4.26±0.35	0.31±0.11	493.5±0.6	95.54±0.08
FT 6	4.36±0.05	4.73±0.26	0.36±0.08	497.3±0.3	94.5±0.05
FT 7	3.94±0.36	4.76±0.21	0.24±0.21	494.9±0.1	93.25±0.13
FT 8	3.85±0.52	4.56±0.48	0.48±0.01	502.2±0.4	91.49±0.26
FT 9	3.84±0.61	4.46±0.37	0.47±0.01	497.8±0.3	96.94±0.04
F10	3.94±0.57	4.46±0.27	0.36±0.12	500.5±0.1	91.52±0.32
FT 11	**4.10±0.21**	**4.66±0.11**	**0.43±0.02**	**501.0±0.1**	**97.54±0.01**
FT 12	4.07±0.26	4.7±0.12	0.44±0.04	497.4±0.4	91.55±0.26

All the values are expressed as a mean ± SD., n = 3 **FT= FINAL TABLET**

Table No. 7: Disintegration Time Data for Irbesartan

Formulation	Disintigretion time(SEC)
FI1	51±0.5
FI2	46±0.9
FI3	35±0.5
FI4	31±0.5

Dissolution of Irbesartan and Simvastatin bilayered tablet:
***In Vitro* Dissolution profile of the formulations of FI 1, FI 2, FI 3 & FI4:**
Optimised formulation T 11:
Graphs of FT 11 formulation:

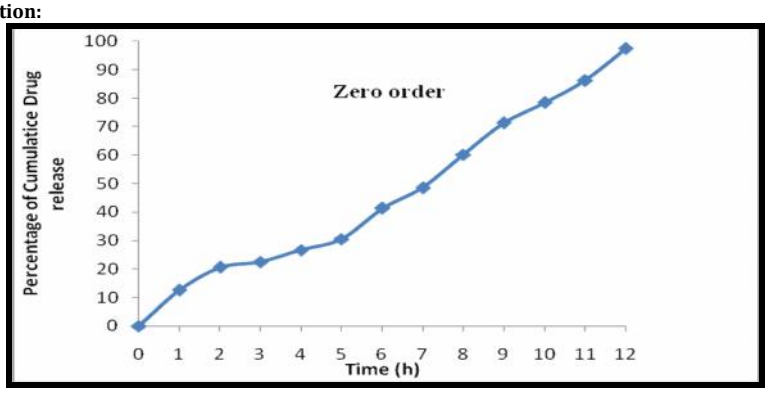

Fig. 5: Zero order kinetics of FT 11 formulation

Released kinetics for all formulations:

Table No. 8: Released kinetics for all formulations

Formulation code	Zero order	First order	Higuchi	Korse – mayer's	
	R^2	R^2	R^2	R^2	n
FT 1	0.9458	0.8365	0.9935	0.9945	0.585
FT 2	0.8592	0.9466	0.9842	0.9510	0.487
FT 3	0.9580	0.8030	0.9437	0.9065	0.560
FT 4	0.8492	0.7829	0.9616	0.9369	0.356
FT 5	0.9842	0.6971	0.9428	0.9873	0.765
FT 6	0.9768	0.9288	0.9518	0.9804	0.787
FT 7	0.9362	0.6567	0.7905	0.8964	0.919
FT 8	0.9540	0.5390	0.8530	0.9531	0.788
FT9	0.9815	0.7181	0.9135	0.9815	1.017
FT10	0.9809	0.8361	0.9461	0.9725	0.755
FT11	**0.9807**	**0.7407**	**0.8740**	**0.9443**	**0.841**
FT12	0.9932	0.7877	0.8859	0.9981	1.153

For matrix tablets, an "n" value near to 0.5 indicates diffusion control and an "n" value near to 1 indicates relaxation or erosion control. The intermediate value suggests that diffusion and erosion contributes to overall release mechanism. A value of "n" for

all matrices studied here was ranged between 2.2899 and 2.9792 indicating an anomalous behavior corresponding to swelling, diffusion and erosion mechanism. It was also observed that highest correlation was found for Peppas log time profile ($R^2 > 0.99$), which indicates the drug release via diffusion mechanism from all matrix formulations.

Stability Studies:

Table No. 9: Data for different evaluation tests of FT11 at the end of 1, 2, 3 month of stability

TIME PERIOD	Hardness (kg/cm2)	Disintegration time(sec)	Drug content (%)
1st month	4.58±0.25	34±0.5	96.93±0.3
2nd month	4.31±0.2	32±0.6	96.28±0.5
3rd month	4.19±0.1	31±0.1	95.6±0.22

All the values are expressed as a mean ± SD., n = 3

***IN-VITRO* dissolution study:**

Table No. 10: *In-vitro* dissolution profile of FT11 at the end of 1, 2, 3 month of stability

Sl. No.	Time (hrs)	% cumulative Drug Release		
		1st month	2nd month	3rd month
0	0	0	0	0
1	1	12.54	12.14	11.86
2	2	20.56	19.98	19.27
3	3	22.53	21.87	21.17
4	4	26.64	25.94	25.37
5	5	30.49	29.97	29.03
6	6	41.28	40.21	39.80
7	7	48.56	47.01	46.59
8	8	60.22	59.08	58.71
9	9	71.24	70.13	69.84
10	10	78.38	76.57	76.28
11	11	86.21	85.72	85.11
12	12	98.65	98.27	97.82

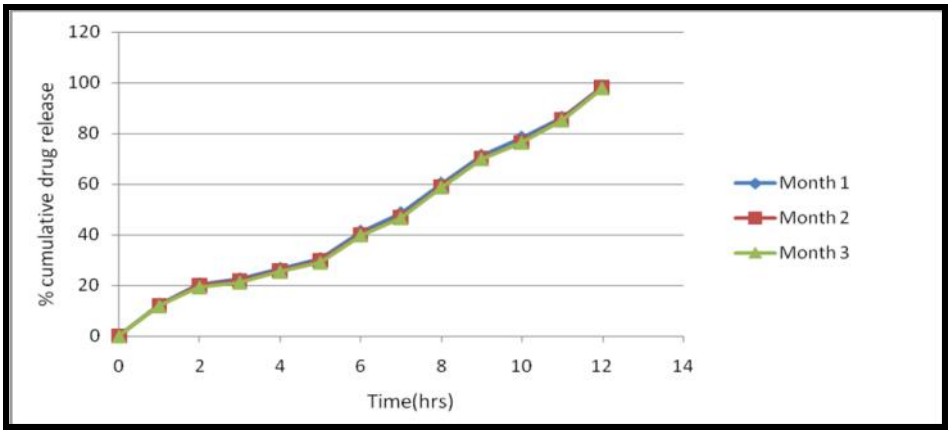

Fig. 6: *In-vitro* dissolution profile of Formulation FT11 at the end of 1, 2, 3 month of stability

DISCUSSIONS

From the **Table 4 & 5**: Evaluation of pre-formulation parameters of Irbesartan and Simvastatin tablet blend was done and the values were found to be within I.P limits with good compressability index. From the **Table 6 & 7** physical evaluation of bilayered tablets was done and all the physical attributes of the prepared tablets were found practically within control (I.P limits).

Drug release studies:

Drug release data were studied to ascertain the kinetics and to compare various formulations, following conclusion was arrived; In formulation FT11 containing simvastatin along with HPMC and CARBOPOL in 1:1 ratio was released 20.56% of drug for 1st two hrs and the release extends up to **12hrs** (98.65%) of drug was released .

Stability studies:

No statistically significant differences were observed in Hardness, percentage drug content and cumulative percentage drug release in optimized formulation at the end of three months of stability studies. So it can be concluded that the formulation is stable for short term storage conditions

CONCLUSION

The objective of this work was to formulate bilayered tablets constituting immediate release layer of Irbesartan and sustained release layer of Simvastatin. Various formulations of Simvastatin layer were prepared using various combinations of excipients. The tablets produced met with the I.P requirement regarding drug content uniformity, hardness, disintegration and friability. All the formulations produced were studied for their drug in dissolution media of 0.1N HCl and 6.8 pH phosphate buffer. Immediate release layer of Irbesartan was prepared by wet granulation method. Sustained release layer of Simvastatin was prepared by Direct Compression method using CARBOPOL, EUDRAGIT and HPMC as release retardants as well as carriers. From the given data formulation **(FT11)** containing HPMC and CARBOPOL (1:1) was found to extend the release up to 12 hrs. Hence it can be

concluded that preparations containing HPMC and CARBOPOL used at 1:1 ratio was found to be the best formulation.

REFERENCES:

1. Allan S. Hoffman. The Origins and Evolution of "Controlled" Drug Delivery Systems, Journal of Controlled Release, **2008**; 132: 153-163.
2. Sungwon Kim, Jong Ho-Kim, Oju Jeon, Ick Chan Kwon, Kinam Park. Engineeered Polymers for Advanced Drug Delivery, European Journal of Pharmaceutics and Biopharmaceutics, **2009**; 71: 420-422.
3. Chien Y. W. "Novel Drug Delivery System", 2nd edn, Revised and expanded, **1992**; Marcel and Dekker Inc. New York, 139-140.
4. Chien Y. W. "Novel Drug Delivery System", 2nd edn, Revised and expanded, **1992**; Marcel and Dekker Inc. New York, 1-2
5. Remington, "The Science and Practice of pharmacy", 20th edn, vol. I, Lippincott William and Wilkins, 903-913.
6. Brahmankar D. M. and Jaiswal S.B. in, "Biopharmaceutics and Pharmacokinetics", "A Treatise", 1st edn, **1995**, Vallabh Prakashan, 347- 352.
7. Lee V. H., Robinson J. R. in, "Sustained and Controlled Release Drug Delivery System ", Marcel Dekker Inc. New York, 71-121, 138-171.
8. Lachman Leon, Liberman H.A. and Kanig J.L. "The Theory and Practice of Industrial pharmacy" 3rd edn, Varghese publishing House, Bombay,p. 430.
9. Brahmankar D. M. and Jaiswal S.B., in, "Biopharmaceutics and Pharmacokinetics", "A Treatise", 1st edn, **1995**, Vallabh Prakashan, 347-371.
10. Lachman Leon, Liberman H.A.and Kanig J.L. "The Theory and Practice of Industrial pharmacy", 3rd edn, Varghese publishing House Bombay, p. 453.
11. Lachman Leon, Liberman H.A.and Kanig J.L. "The Theory and Practice ofIndustrial pharmacy", 3rd edn, Varghese publishing House, Bombay, p. 443.
12. Ruggero Bettini, www.medfarm uniforit/pharmaco/itcis/Erasmus/ erasm13, html.
13. V. H. Lee, J. R. Robinson. In, "Sustained and Controlled Release Drug DeliverySystem ," Marcel Dekker Inc. New York, 71-121.
14. J. Lapidus, N. G. Lordi. in, "Journal of Pharmaceutical Science", **1991**; 86.
15. Liberman, H. A. "Pharmaceutical Dosage Form; Tablets", 2nd edn, Vol. I, p. 136.
16. Liberman, H. A. "Pharmaceutical Dosage Form; Tablets", 2nd edn, Vol. I, 201-213.

How to cite this article:

Naikar Nuzhathullah et al.,: Design, Fabrication and Invitro Evaluation of Irbesartan and Simvastatin Bilayered tablets. J. Pharm. Res., 2014; 3(10): 198-203.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil