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Formulation Development of Fixed Dose Combination of Metoprolol Succinate Extended Release Pellets and Atorvastatin Calcium Immediate Release Drugs

Anil Kumar chandragiri [1]*,. Thirupathi Kaluvala[1], Vijaykumar Nagabandi [2] Kranthi Raju palle[1]

1. *University College of Pharmaceutical Sciences, Satavahana University, Karimnagar*
2. St. Peters institute of Pharmaceutical sciences, Hanmakonda, Warangal

ABSTRACT

The main objective of current research work was to develop a stable pharmaceutically equivalent combined dosage form of immediate release Atorvastatin calcium and extended release Metoprolol succinate formulation, which is comparable to that of innovator's. Combination therapy affords the physician and the patient the opportunity to more effectively treat diseases that may stem from more than one cause. When used correctly and appropriately, combination therapy leads to better outcomes than mono therapy by treating more than one cause of the disease and/or by synergistically enhancing the action of one of the component drugs. The purpose of the study was to develop a capsule of Atorvastatin calcium (IR) and Metoprolol succinate (ER) having different release pattern, which is indicated for the management of hypertension. The study was planned in three stages. In the first stage three batches (A1, A2, and A3) of immediate release blend of Atorvastatin calcium was prepared using pre-gelatinized starch as super disintegrate. In the second stage, nine batches (M1-M9) of Metoprolol succinate sustained release pellets were prepared using various polymers and levels of coatings as rate retardants. Preformulation studies were performed after granulation. In the third stage capsules were evaluated for weight variation, drug content, and disintegration time and *in vitro* drug release using RP-HPLC. FTIR studies revealed no disturbances in the principle peaks of pure drugs and it confirms the integrity and compatibility of pure drugs with their excipients.

Keywords: Atorvastatin calcium, Metoprolol succinate, Coating, Pellets and HPLC.

*Corresponding Author Email: chanil123@gmail.com
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INTRODUCTION

Hypertension is the most common cardiovascular disease. The prevalence of hypertension increases with advancing age[1]. Arterial pressure is the product of cardiac output and peripheral vascular resistance. Drugs lower blood pressure by actions on peripheral resistance, cardiac output, or both. Drugs may reduce the cardiac output by inhibiting myocardial contractility or by decreasing ventricular filling pressure. Drugs can reduce peripheral resistance by acting on smooth muscle to cause relaxation of resistance vessels or by interfering with the activity of systems that produce constriction of resistance vessels (*e.g.*, the sympathetic nervous system). In patients with isolated systolic hypertension, complex hemodynamic in a rigid arterial system contribute to increased blood pressure; drug effects may be mediated by changes in peripheral resistance but also *via* effects on large artery stiffness[2]. Metoprolol succinate, β1-selective adrenergic receptor blocking agent used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism and in the prophylactic treatment of migraine. The half-life of drug is relatively short approximately 4-6hrs and in normal course of therapy drug administration is required every 4-6hrs, thus warrants the use of extended release

formulation for prolong action and to improve patient compliance [3]. Anti lipideamic agents are an important group of drugs for the treatment of ischemia and hypertension. Atorvastatin calcium is a HMG Co-A inhibitor and has a longer duration of action and the initial effects are cumulative over many days and more over for patient compliance in case of anti angina patients, a rapid onset of action is necessary for immediate pain relief. In recent times, multi-layer matrix tablets are gaining importance in the design of oral controlled drug delivery systems. The combined dosage forms are preferred for the following reasons: to co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for staged drug release, IR and ER in the same capsule, for chronic condition requiring repeated dosing.

In the present study a combination drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each. The rational for combination therapy is to encourage the use of lower dose of drug to reduce the patient's blood pressure, minimize dose dependent side effects and adverse reactions[4].

MATERIALS AND METHOD

Materials

The following materials were obtained from The Madras Pharmaceuticals as gift samples

Metoprolol Succinate USP, Atorvastatin Calcium IP, Hard gelatin capsules, Sugar globules (#20/25), Ethyl cellulose, Methyl cellulose, Micro crystalline cellulose, Spheres CP203, Hydroxy propyl methyl cellulose (Low viscosity), Hydroxy propyl methyl cellulose (High viscosity) HPMC K4M, HPMC K15cps, Talc, Tri Ethyl Citrate, Acetyl Tri Butyl Citrate, Lactose IP, Caco3 IP, Cross Carmellose Sodium USP/NF, Polysorbate 80 IP, Hydroxy Propyl Cellulose USP/NF, Lactose (DT) IP, Magnesium Stearate, Partially Gelatinized Starch, PGS (Fully), Light Mg O, Iso propyl alcohol all the materials were analytical grade.

Methods of Preparation

The study was planned in three stages

1. Formulation of Atorvastatin calcium immediate release blend and evaluation.
2. Formulation of Metoprolol succinate extended release pellets and evaluation.
3. Optimized prototype formulation filled in to capsules of IR and ER part and evaluation[5].

Formulation of Atorvastatin calcium immediate release layer

In the first stage, three batches (A1, A2 and A3) of immediate release blend of Atorvastatin calcium were prepared. **Table.1.** All the materials were sifted through appropriate sieve (#30) and mixed in RMG, binding solution was prepared by dissolving Polysorbate 80 in IPA and HPC was added with continuous stirring until to get homogeneous mixture and was added to the blend until dough mass is obtained. Then the granules were dried at 50°C for 10 minutes by using FBD and sifted the granules by using 30#. Lubrication was done in double cone blender and cross carmellose sodium USP/NF, Lactose (DT) IP were added mixed for 25 minutes. To this magnesium stearate was added and mixed for 5 minutes and compressed using 5mm punches.

Table 1 Atorvastatin Calcium IR blend preparation

Ingredients	F:01(mg)	F:02*(mg)	F:03*(mg)
Atorvastatin Calcium	10.84	10.84	10.92
Lactose IP	75.16	-	-
Caco3 IP	11.0	-	-
CCS USP/NF	3.0	-	-
Polysorbate 80 IP	2.5	-	-
HPC USP/NF	3.5	-	-
IPA	qs	-	-
Lactose (DT) IP	8.0	-	-
Magnesium Stearate	1.0	-	-
CCS USP/NF	5.0	-	-
PGS – (Partially)	–	117.48	97.4
PGS – (Fully)	–	11.48	11.48
Light Mg O	–	2	2

* Indicates blend formulation

FORMULATION OF METOPROLOL SUCCINATE (MS) EXTENDED RELEASE PELLETS

In the second stage nine batches (M1-M9) of Metoprolol succinate extended release pellets contains different stages of coating were prepared and the formula was given in the **Table 2 & 3** and parameters used for fluidized bed coating are given in **Table 4**

Sealing coating stage

Ethyl cellulose- 10cps was dispersed uniformly in IPA; stirring was done for 20 mins. Later the remaining of the solution was added after stirring, M.C was added to it. Stirring was continued for another 20 min and then used for coating**.**

Drug loading stage:

All the raw materials were dispensed. Required quantity of purified water was heated to 70 – 80^{o}c. Metoprolol succinate was added to above mixer under stirring. Specified quantity of HPMC (Low Viscosity) was added in purified water to form a clear solution. The M.C.C Spheres (25/40) were coated using above solution by fluidized bed coater.

Sub coating stage:

Specified quantity of HPMC (High viscosity) was dissolved in purified water under stirring to form a clear solution. The drug loaded pellets prepared in step were sub coated using sub coating solution using fluidized bed coater.

Extended release coating stage:

Specified amount of IPA was taken & dissolved in ethyl cellulose under stirring. HPMC (Low viscosity) was dispersed in the required quantity water & stirred to form clear solution. Required quantity of TEC was added to above step and stirred it for appropriate time. Coated the sub coated pellets prepared in sub coating stage using coating solution to get extended release pellets.

Table 2 MS Formulation Development

Ingredients	M1	M2	M3	M4	M5	M6	M7	M8	M9
Seal coating stage									
Sugar globules (#20/25)		320	–	–	–	–	–	–	–
EC		16	–	–	–	–	–	–	–
IPA		250	–	–	–	–	–	–	–
M.C		83	–	–	–	–	–	–	–
Drug loading stage									
Metoprolol succinate	300	350	350	300	300	350	1166.66	–	2333.23
Seal coated pellets	–	300	–	–	–	–	–	–	–
M.C.C Spheres CP203	–	–	-	300	300	–	–	–	–
M.C.C Spheres (CP 507)	–	-	300	-	–	300	1000	–	2000
HPMC (Low viscosity)	-	10	10	36(12%)	36	10	33.33	–	66.66
Purified Water	–	165	–	1380	136	165	2500	–	5000

Sub coating stage									
D. L. P	–	600	–	–	–	–	2000	–	2000
HPMC (High viscosity)	–	30	–	–	–	–	100	–	100
HPMC 15cps	-	-	-	–	–	–	1500	–	1500
HPMC K4M	-	-	-						
Purified water	–	350	–						
Extend Release Coating									
D. L. P	250	-	–	200	200	300	–	–	–
S.C.P	–	300	–	–	–	–	1000	1000	1000
HPMC (Low viscosity)	–	10	–	–	–	17.5	25	20	20
HPMC 15cps	-	-	-	18.65	–	–	–	–	–
HPMC K4M	-	-	-	–	20	–	–	–	–
EC 10cps	–	33	50	83.94	78	70	80	70	83.33
Sure lease	150 (50%)	–	–	–	–	–	–	–	–
IPA	–	550	130	494.61	459	111	1600	1600	1600
M. C	–	180	–	1967.39	182	370	–	–	–
ATBC	–	6	5	–	–	–	13.33	13.33	–
TEC	–	–	–	11.40	9.4	3.5	–	–	12.5
Talc	200	–	–	–	9.8	–	–	–	–
Purified water	–	–	–	-	-	-	400	400	400

Table.3 Optimized formula (M9) of MS pellets: Batch size - 1.0kg, 107mg/caps

Sl.No	Ingredients	Qty/batch (g)
Drug Loading Pellets		
1	Metoprolol succinate	2333.23
2	M.C.C Sphères (25/40)	2000
3	HPMC (Low viscosity)	66.66
4	Purified water	5000
Sub coating Pellets		
5	DLP	2000
6	HPMC (High viscosity)	100
7	Purified water	1500
ER coating pellets		
8	Drug Loaded pellets	1000
9	Ethyl cellulose	83.33
10	HPMC (Low viscosity)	20
11	TEC	12.5
12	IPA	1600
13	Purified water	400

Table 4 Parameters for coating using as a fluidized bed coater

S.No	Parameters	Set value
1.	Inlet air temp	40 - 50ºc
2.	Pellet Bed temp	32 - 38ºc
3.	Atomization air pressure	2.0 – 3.0 kg/cm^2
4.	Peristaltic pump RPM	Shall be monitored
5.	Spray rate	4–6g/min/kg of pellets
6.	Blower RPM	1500-2000RPM

Filling in capsules:

Optimized formulation (03) of Atarvostatin calcium and optimized formulation of (M9) metoprolol succinate pellets were filled in to size 2 hard gelatin capsules, using automated capsule machine.

Evaluation of Granules Micromeritic Properties

The prepared granules were evaluated for bulk density, tapped density, Carr's index, Angle of Repose, Hausner's ratio, particle size distribution and content uniformity[6, 7].

Methods of Evaluation

Assay: Assay was done by HPLC and the conditions are given below

Column: Inertsil ODS C18, 250 x 4.6mm

Detector Wavelength: 280mm

Flow Rate: 1.0ml/min

Injection Volume: 50µl

Mobile Phase: Buffer: Acetonitrile (60:40)

Procedure

Fifty micro liter sample preparation was injected into the liquid chromatography and the chromatogram was recorded. The responses for the major peaks were recorded. The dissolve quantity of Atorvastatin calcium in sixty minutes and Metoprolol Succinate in one, two, four, eight, twelve ,sixteen and twenty hour from the peak areas of standard and sample preparation and percentage of potency of working standards used were calculated[8-10].

***In-vitro* Drug Release Studies**

In vitro drug release studies Metoprolol succinate from the formulated extended release pellets was carried out in tablet dissolution tester Electro lab USP- II put 6 capsules in to sinkers and drop individually in six dissolution flasks containing 500ml of medium that has been equilibrated to 37ºc±0.5ºc. Collect the sample after specified time, withdraw sample from a zone mid way between the surface of the medium and top of the rotating blade and not less than 1 cm from the vessel wall. For Atorvastatin calcium put 6 capsules in to sinkers and drop individually in six dissolution flasks containing 900ml of medium that has been equilibrated to 37ºc±0.5ºc.Collect the sample after specified time, withdraw sample from a zone mid way between the surface of the medium and top of the rotating blade and not less than 1 cm from the vessel wall and filter through 0.45µ membrane filter separately inject blank, standard for 5 times and test preparation in to liquid chromatogram and record the areas for major peaks. In vitro dissolution conditions are given in Table 5

Table 5 *In vitro* dissolution conditions

	Apparatus	Medium	Sampling interval	RPM
Metoprolol succinate	USP apparatus II (paddle)	pH 6.8 phosphate buffer, 500ml	1,2,4,8,12,16,20 hrs	50
Atorvastatin calcium	USP apparatus II (paddle)	pH 6.8 phosphate buffer, 900ml	5,10,20,30,45,60 mins	75

RESULTS AND DISCUSSION

Results of Granules Micromeritic Properties:

Prepared granules were evaluated for various micromeritic properties results of which are given Table 6-8**.**

Table 6 Evaluation tests for Atorvastatin calcium blend

Formulation Code	Angle of repose(θ)	Bulk Density(g/cm^3)	Tapped Density(g/cm^3)	Carr's Index	Hauser's Ratio
A:03A	24°12″±19″	0.483±0.02	0.584±0.06	17.29±0.3	1.20±0.02
A:03B	23°33″±30″	0.487±0.04	0.564±0.04	13.65±0.5	1.15±0.06

Table 7 Evaluation tests for Metoprolol succinate pellets

Formulation	For DLP*		For SCP*		For ERP*	
	Bulk density (gm/cm3)	Tapped density (gm/ cm3)	(Bulk density) (gm/ cm3)	Tapped density (gm/ cm3)	Bulk density (gm/ cm3)	Tapped density (gm/ cm3)
M:09A	0.844	0.844	0.847	0.847	0.850	0.850
M09B	0.824	0.824	0.828	0.828	0.833	0.833

***** DLP – Drug Layered Pellets; SCP- Sugar Coated Pellets; ERP – Extended Release Pellets

Table 8 Particle size distribution of Metoprolol succinate:

S.No	Mesh size	Empty sieves wt (gms)	Formulation:09A Loaded sieves wt(gms)	Formulation:09B Loaded sieves wt(gms)	% of pellets retained	% of pellets retained
1.	#18	187.1	188.33	189	4.90	7.57
2.	#20	184.7	208.07	206.2	93.11	85.66
3.	#25	186.4	187.4	188.32	3.98	7.65

% of pellets retained = Difference/Input*100

Content Uniformity:

Results of content uniformity studies are given in Table 9.

Table 9 Content uniformity of Metoprolol succinate:

Sl. No	Formulation:09A		Formulation:09B	
	Metoprolol Succinate	Atorvastatin Calcium	Metoprolol Succinate	Atorvastatin Calcium
1	97.9	94.9	100.9	88.9
2	94.5	91.1	101.5	96.4
3	96.7	93.3	102.8	92.5
4	101.5	90.9	87.7	87.8
5	96.3	88.9	101	88.8
6	98.9	90.8	98.3	93.4

7	98.5	94.4	100.9	91.7
8	97.6	93.9	101.6	91.1
9	95.1	90.2	99.6	96.6
10	96.2	92.6	101.9	93.5
Avg	97.32	92.1	99.62	92.07

***In Vitro* Drug Release Studies:**

Prepared capsules were evaluated for *in vitro* drug release. Results are shown in in graph no.1, 2 and 3. The pharmacokinetic release profiles were shown in graphs 4, 5 and 6. R^2 values obtained are tabulated in table 10. According to the results they have are following higuchi model mechanism of drug release diffusion.

In this study, the formulation of fixed dose combination of Metoprolol succinate extended release and Atorvastatin calcium immediate release was developed. For preparation of Metoprolol succinate extended release formulation, a series of polymers were used to control the release of drug. Initially trails were made for optimizing the process with the following polymers. In the first trial (F: 01) sure lease (aqueous dispersion of Ethyl Cellulose) was used as a controlling polymer. It was observed that, sure lease was not at all effective in controlling the release of metoprolol succinate as it showed burst release of the drug in the initial (1, 2 & 3rd) hrs itself. So it is not a suitable polymer to make an extended release dosage form. So instead of sure lease, a combination of hydrophilic and hydrophobic polymers was used for getting the desired release.

In this approach, the hydrophilic polymer forms a channel for the diffusion of the drug and hydrophobic polymers controls the release of the drug. In the second trial (F: 02), sugar beads were selected as core material. This requires seal coating to minimize the fragmentation of globules. But, inspite of seal coating, fragmentation was observed during drug loading and nozzle blocking was also observed which results in drug loss. Hence, sugar globules were not suitable for making pellets in fluid bed coater. In the third trial (F: 03), matrix type of delivery was followed. In this approach, the drug and the polymer were sprayed together on the MCC pellets and these matrix pellets showed the drug release of 97% within 1 hour. So, the matrix type of delivery was not suitable for making ER pellets, because it showed a rapid release of the drug from matrix when compared with the membrane controlled (reservoir controlled) type of delivery. Hence by this approach, it was concluded that the reservoir type of delivery is appropriate for making pellets.

The following trials were done by the combination of hydrophilic (HPMC) and hydrophobic (EC) polymers, along with ATBC & TEC as plasticizers and IPA, M.C & Purified

water as solvents in ER coating with change of concentrations. In the Fourth trail (F: 04), combination of EC and HPMC 15CPS in the ratio of 4.5:1 was followed, but the release of drug from the pellets was more, when compared with innovator release profile. So HPMC 15 CPS was replaced with HPMC K4M (high viscosity grade of HPMC) in the ratio of 3.9:1 (EC and HPMC K4M) in Fifth Trail (F: 05), but it was observed that the drug release at 16th & 20th hours was less, when compared with innovator.

To get desired release profile, the combination of HPMC 3 CPS and EC 10 CPS was used in the following ratios. In this trail (F: 06), 30% build up of EC 10-CPS and HPMC 3 CPS in the ratio of 4:1 was given as ER coating, but the drug release was observed after 12 hours only. In the next trail (F: 07), TEC was replaced with ATBC and methylene chloride with purified water & 35% build up of EC and HPMC 3CPS in 3.2:1 ratio was given, but the release of drug was found to be less. It was concluded to reduce the buildup of EC and HPMC. In this trail (F: 08), attempt was made with 30% build up of EC and HPMC 3CPS in 3.5:1 ratio.

The release of drug was found to be satisfactory and matched with innovator profile, but the release at 1st and at 2nd hours is less when compared with innovator. It was concluded to replace ATBC with TEC (F: 09) to get better release profile. The individual formulations of Atorvastatin calcium Immediate release and Metoprolol succinate Extended release were filled in Hard gelatin capsules of size#2 by using automatic capsule filling machine.

Prior to capsule preparation the blend were evaluated for angle of repose, bulk density, tapped density, Carr's index, Hauser's ratio and the results are given Table No.5. The capsules were also evaluated for drug content and the results are given Table No.8 and the results of *in vitro* drug release are given Table no.10-12. They showed that all batches had good flow property. Hence all batches were taken up for further studies. The average weight, hardness, thickness for the prepared granules were within the limits and had faster initial *in vitro* drug release.

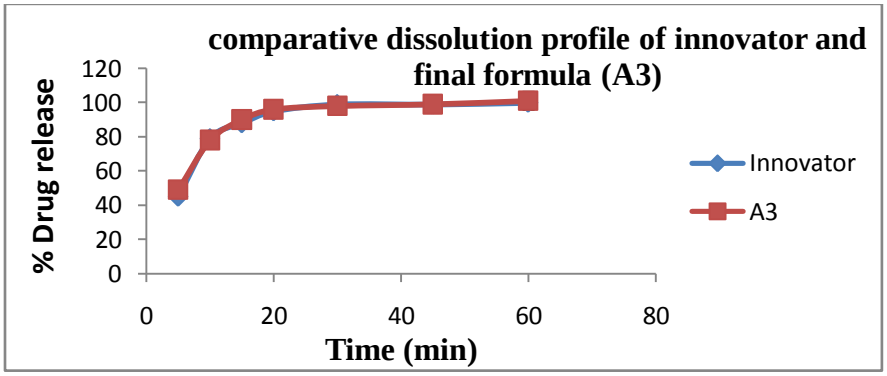

Figure 1: Comparative dissolution of innovator and optimized formula (A3) of Atorvastatin calcium blend

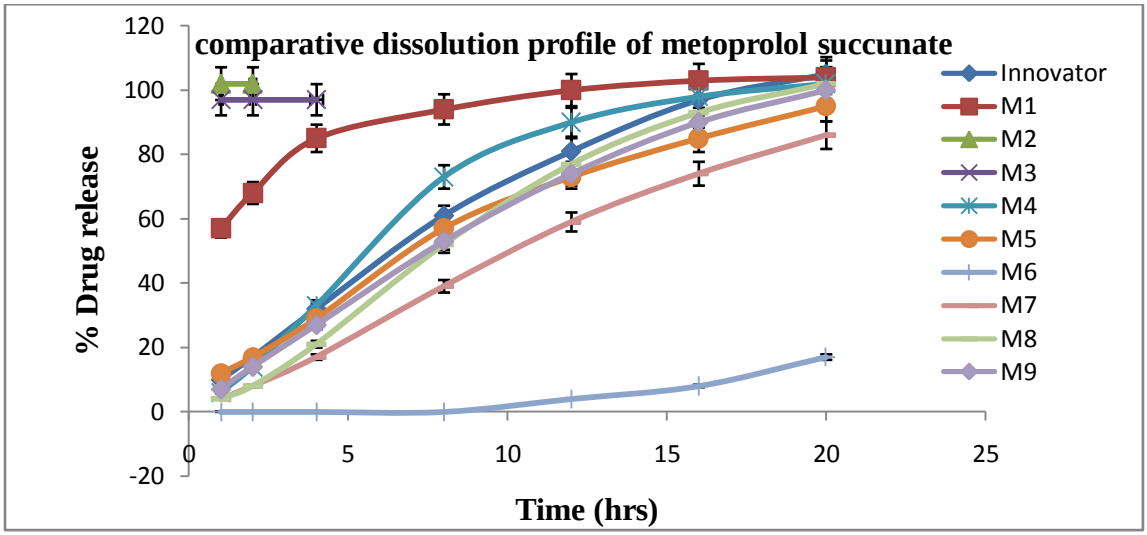

Figure 2: Comparative dissolution of innovator and different formulations (M1-M9) of metoprolol succinate pellets

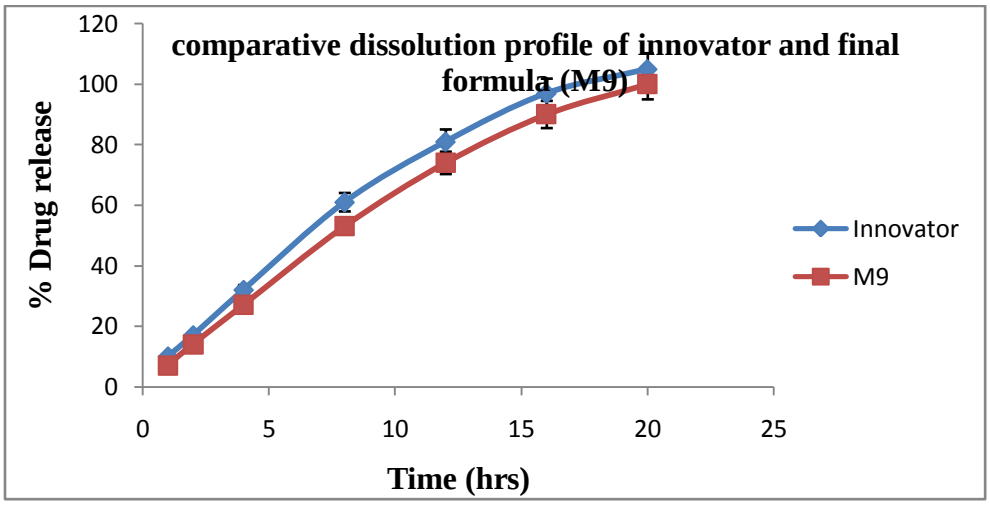

Figure 3: Comparative dissolution of innovator and optimized formula (M9) of metoprolol succinate pellets

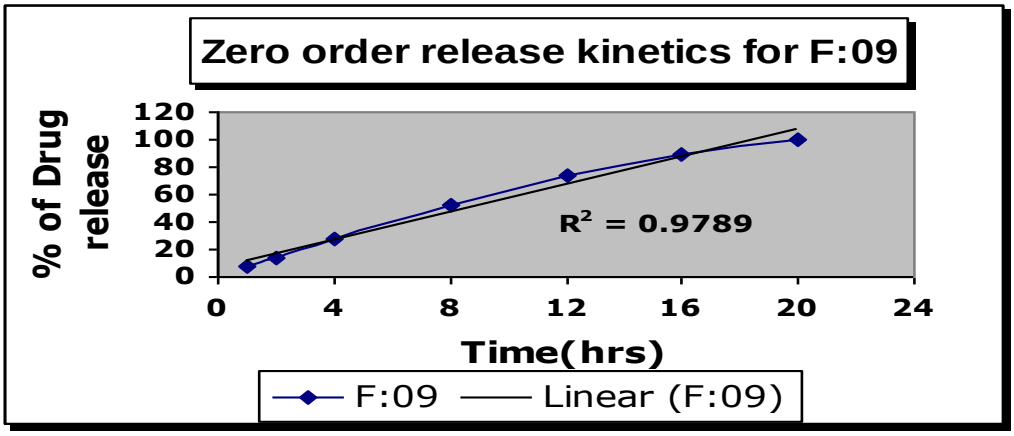

Figure 4: Zero order release kinetics (% of Drug release Vs Time)

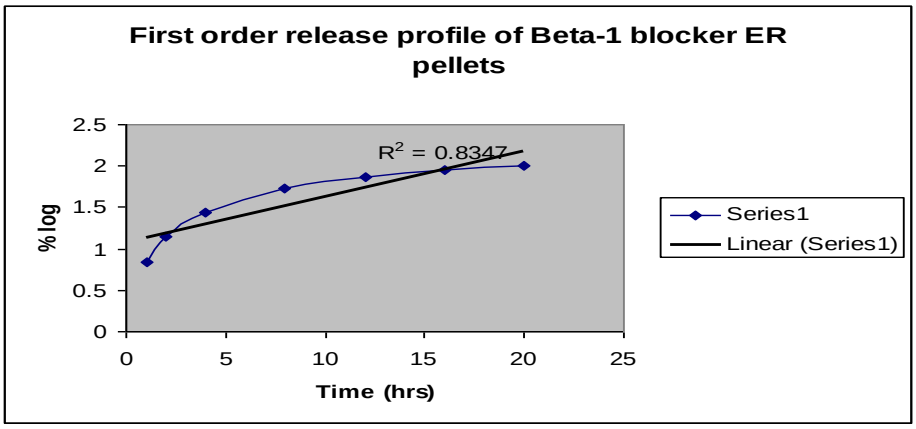

Figure 5: First order release kinetics (% log vs time)

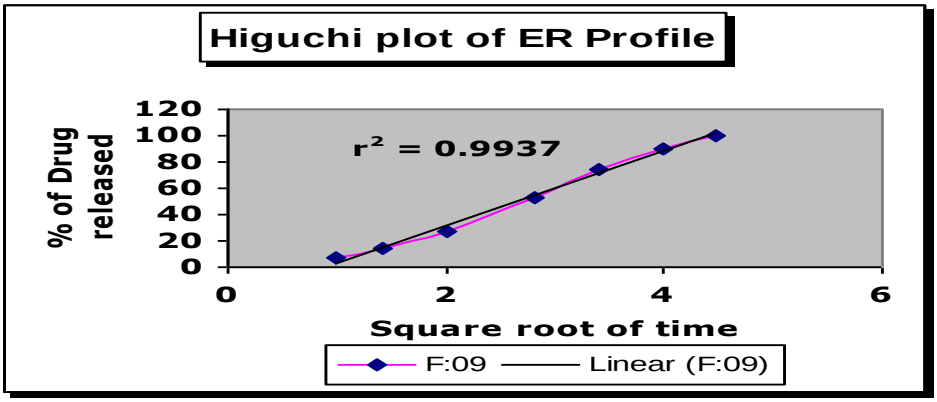

Figure 6: Higuchi plot (% of Drug released vs time)

Table 10 Comparative pharmacokinetic release studies of Metoprolol Succinate optimized formula (M9)

	Zero order kinetics	First order kinetics	Higuchi plot
r^2 value	0.9789	0.8347	0.9937

CONCLUSION

In this study, the formulation of fixed dose combination of Metoprolol succinate extended release and Atorvastatin calcium immediate release was developed. For preparation of Atorvastatin calcium immediate release formulation, we tried out the tablet approach initially, due to its more thickness problems were encountered during filling. Because of above problems we tried the blend approach (A3) instead of tablet approach release profile, impurities and filling found to be satisfactory. Based on the observation, it was concluded that batch A3 and B9 exhibited desirable properties and optimized drug release .The *in- vitro* drug release of batch A3 and B9 was followed the USP limits. Hence batch A3 and B9 was considered as a desirable batch. The results demonstrated the effective use of capsules of Metoprolol succinate and Atorvastatin calcium as an ideal drug release formulation for treatment of hypertension.

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