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Inlay tablet of Atorvastatin calcium with sustained release Metoprolol tartarate

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ABSTRACT

The objective of this study was to design a dual retard technique of once daily Inlay tablet of Atorvastatin calcium as Immediate Release (IR) formulation with Matrix tablet of Metoprolol tartarate as Sustained release (SR) formulation for Hypertension and Atherosclerosis. The Inlay tablet was prepared by Wet granulation method. The Compatibility of the drug with various excipients was studied by Differential scanning calorimetry (DSC). The formulations were developed by using polymers like Guar gum, Eudragit, HPMC for sustained release layer and Sodium starch glycolate, Cross povidone, Cross carmellose sodium as Super disintegrants for immediate release layer. Six formulations (F1-F6) were prepared and evaluated for various parameters like Thickness, Hardness, Weight variation, Disintegration, Swelling Erosion behavior, Simultaneous analysis by both UV and HPLC, *In vitro* release and Stability studies at 40º±2ºC, RH 70±5%. Among the six formulations (F1-F6), F4 possess expected release pattern in both immediate release layer and sustained release layer. Further from the Release kinetics it was revealed that the drug release for formulation F4 follows Zero order. Thus the study concludes that the formulation can overcome the disadvantages of other multilayered tablets and can be used to treat the patients having high blood pressure with Hyperlipidemia that plays major risk factors for CHD.

Key words: Inlay tablet, Matrix tablet, Hydroxypropyl methylcellulose, Metoprolol tartarate, Atorvastatin calcium, Hypertension.

INTRODUCTION

Hypertension is the most common cardiovascular disease and it can be defined as a sustained increase in blood pressure above the normal level (120/90 mm Hg) to (=140/90 mm Hg) level.(1, 2) Hypertension is the primary cause of stroke, major risk factor for coronary artery disease like atherosclerosis and its complications, and is a major contributor to cardiac failure, renal insufficiency and dissecting aortic aneurysm.(3,4).

Atherosclerosis is the deposition or formation of plaques of fat in the walls of the arteries and forms major conventional risk factors for CHD (5). Hypertension with Hyperlipidemia is most complicated cardiovascular diseases, which should be treated simultaneously to prevent morbidity rate. (6) The combination of ß-blockers and Statins reduce cardiovascular events and progression of Carotid Intima Media thickness (IMT).(7) This suggests that ß-blockers and Statins have a favorable effect on Atherosclerosis development(8).

Metoprolol is a ß1-selective antagonist and numbers of clinical trials have demonstrated the beneficial effects of Metoprolol therapy in heart failure, with decreased mortality due to both reductions in sudden death and death from worsening of heart failure. The Statins are the most effective and best tolerated agents for treating Dyslipidemia. These drugs are competitive inhibitors of 3-Hydroxy-3-Methylglutaryl Coenzyme A (HMG-CoA) reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis. The efficacy and safety of the statins in reducing fatal and reducing triglyceride levels caused by elevated VLDL levels and nonfatal CHD events, Strokes and total mortality are well established(9).

Inlay tablets is a type of layered tablet .While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compress the whole tablet. It is a novel platform technology for decreasing the mechanical shear on double compressed products which can lead to decrease in unknown process related impurities. Incompatible drugs can also be designed by this dosage form.

This Sustained release dosage form reduces the frequency of dosing, reduce pill burden and thus improve the patient compliance. It also results in less fluctuation of drug in circulating blood level. Most importantly, because of prolonged duration of action, it shall produce a strict control of blood pressure and consequently less hypertension complication .The goal of this therapy is to treat the patient having high blood pressure with Hyperlipidemia that plays major risk factors for CHD.(10)

MATERIALS AND EQUIPMENTS:

The drugs Metoprolol tartarate and Atorvastatin calcium is purchased from Milton labs, Pondicherry. Polymers and other excipients were obtained from Novel drugs Pvt. Ltd, Trichy. 23- Station Rotary Tablet Punching Machine (Rimek) with 8×32'', 16×32''was used for T ablet punching.UV-Spectrophotometer (Shimadzu 1700), DSC (Perkin - Elmer DSC 60), HPLC (Spinchrome) and Dissolution apparatus Electrolab (USP 24) was used for analytical processes.

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METHODS

Compatibility Studies:

Compatibility studies between the drug and the polymers were performed by using Differential scanning calorimetry (DSC) technique to determine whether there is any incompatibility between the drug and ingredients.

Preparation of Inlay Tablet:

Both Immediate release core tablet and Sustained release cup portion with different polymers proportions are prepared by Wet granulation technique.

A. Formulation of Immediate Release (IR) Core Tablet:

Atorvastatin calcium along with super disintegrants like Sodium starch glycolate, Cross povidone, Cross carmellose sodium and excipients as in (Table no: 1) was mixed geometrically in mortar and pestle and passed through sieve # 44 to attain uniformity and starch is used as binder and added to dry mix to form a mass which is passed through sieve # 10 and then with sieve # 22 to form a granules. Granules are dried in tray drier at 60°C and it is lubricated by 1% Magnesium stearate. Finally the granule was compressed by using 8×32''round flat plain upper and lower punches. (11)

Table 1: Formulation of IR Atorvastatin Calcium Granules

S.no	Ingredient (mg/ tablet)	FA_1	FA_2	FA_3	FA_4	FA_5	FA_6
Dry mix							
1	Atorvastatin calcium	10	10	10	10	10	10
2	Lactose	55	55	55	50	50	50
3	Starch	30	30	30	30	30	30
Binder solution							
4	Starch mucilage	q.s	q.s	q.s	q.s	q.s	q.s
5	Water	q.s	q.s	q.s	q.s	q.s	q.s
Blending							
5	Sodium starch glycolate	4	-	-	9	-	-
6	Cross povidone	-	4	-	-	9	-
7	Cross carmellose sodium	-	-	4	-	-	9
Lubrication							
8	Magnesium stearate	1	1	1	1	1	1
Total core tablet weight =100 mg							

B. Formulation of Sustained release (SR) outer cup portion:

Metoprolol tartarate was added with release retarding agent like Guar gum, HPMC K 100 and K 4 M, Eudragit S 100 and L 100 and excipients as in (T able no:2) and Wet granulation technique was followed as same as core tablet. Finally granules were lubricated with 2% talc and 1% magnesium stearate. (12)

C. Formulation of Inlay Tablet:

The final formulation of Inlay tablet includes both SR and IR granules. The granules of Metoprolol tartarate were filled in the dye and already punched

Table 2: Formulation of SR Metoprolol Tartarate Granules

S.No	Ingredient mg/ tablet	FM1	FM2	FM3	FM4	FM5	FM6
Dry mix							
1	Metoprolol tartarate	150	150	150	150	150	150
2	Eudragit L 100	120	-	-	-	-	-
3	Eudragit S 100	-	120	-	-		60
4	Guar gum	-	-	-	120	-	-
5	HPMC K 100	-	-	120	-	-	-
6	HPMC K 4 M	-	-	-	-	120	60
7	Lactose	118	118	118	118	118	118
Binder solution							
8	Starch mucilage	q.s	q.s	q.s	q.s	q.s	q.s
9	Water	q.s	q.s	q.s	q.s	q.s	q.s
Lubrication							
10	Talc	2%	2%	2%	2%	2%	2%
11	Magnesium stearate	1%	1%	1%	1%	1%	1%
Total outer cup portion weight =400mg							

Atorvastatin calcium were being placed centrally over the SR granules and it was compressed by using 16×32''round flat plain upper and lower punches. Feed frame was adjusted until optimized weight and hardness of the tablet results and Inlay tablets were formulated. **(**13)

PREFORMULATION STUDIES :

DSC THERMOGRAM STUDIES:

Procedure:
Differential Scanning Calorimetry was performed in order to characterize the physical state of drug and polymer. Thermogram was obtained using DSC. About 5mg of sample was weighed, crimped into an aluminum pan and analyzed at a scanning temperature range from 50 ºC - 300ºC at the heating rate of 2ºC/min under nitrogen flow of 25ml/min.

The DSC thermogram obtained shows that the melting point obtained in pure drug and drug mixture was similar in range which infers that, no drug polymer interaction was there in the formulation and the drug was compatible with excipients. (14)

EVALUATION OF THE GRANULES

Bulk density and tapped density
25 g of Atorvastatin calcium granules, 25 g of Metoprolol tartarate granules were weighed respectively and transferred into a graduated measuring cylinder via a large funnel and the volume of the powder was measured. Tapped volume of the powder was measured by tapping method. The bulk density of the granules is calculated by given formula.

LBD = Wt of Powder / Vol. of Powder
TBD = Wt of Powder / Tapped Vol. of Powder

Flow properties of the powder:

Compressibility index and Hausner's ratio
The compressibility index and Hausner's ratio have become the simple, fast and popular methods of predicating powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the Hausner's ratio are determined by measuring both the bulk volume and the tapped volume of granules as follows.

Compressibility Index =100 X Vo-Vf/Vo
Hausner's Ratio = Vo/Vf

Angle of Repose
The angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. Angle of repose of granules is done by fixed funnel method and is calculated by using following formula,

$\theta = T an^{-1} h/r$

Where, h = height of the pile; r = radius of the pile
The tangent of the angle is equal to the coefficient of friction (M) between the particles

PHYSICAL EVALUATION OF TABLETS

Weight variation
Tablet designed to contain a specific amount of drug .T he weight of the tablet being made is routinely measured to ensure the tablet contains the proper amount of drug. 20 tablets were selected randomly from each batch and average weight was calculated. Then the deviation (as per IP limit ±5% for 500 mg tablet) of individual weights from the average weight and then standard deviation was calculated. (15)

Hardness
The Monsanto hardness tester consists of a barrel containing a compressible spring held between two plungers. Then lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is then forced against or spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force and the force of fracture is recorded. (16)

Friability
The laboratory friability tester is known as the Roche friabilator. 10 tablets are weighed and placed in the plastic chamber which revolves at 25 rpm dropping the tablets a distance of six-inches with each revolution which is operated for 100 revolutions. The tablets are then dusted and reweighed to find out the % of loss in weight (as per IP limit it should be <1%). The friability of the tablet is determined by the formula given below. Then average hardness and standard deviation was calculated.

$$\text{Friability} = \frac{\text{Final Weight-initial weight}}{\text{Initial weight}} \times 100$$

Determination of Thickness
Thicknesses of five randomly selected tablets from each batch were measured with a Vernier caliper. Then the average Thickness and standard deviation were calculated. Tablet thickness should be controlled within 5% variation of a standard value. (17, 18)

Assay:
Chromatographic condition
Column :C_{18} column
Diluent: Acetonitrile :Water (1:1)
Mobile Phase : Phosphate buffer (pH – 6.8): Acetonitrile (80:20)
Detection Wavelength :264 nm
Flow rate :1ml/min
Mode of operation :Isocratic elution technique.
Detector :UV/Visible

Preparation of standard solution:
An accurately weighed quantity of Atorvastatin calcium equivalent to Atorvastatin 10 mg is taken in 10 ml volumetric flask and dissolved with mobile phase that having a concentration of 1000µg/ ml. From this stock solution 1ml is taken and the volume is made up to 10ml with mobile phase to get a concentration of 100µg/ ml Atorvastatin (solution A). Then the solution was filtered through a syringe filter. 20µl of this solution were injected under respective chromatographic conditions. Same procedure is followed for Metoprolol tartarate also (solution B). Both A and B solutions are mixed, filtered, degassed and it was injected at a flow rate of 1ml per minute and detected at wave length of 264 nm. Amount and percentage of drug release was calculated by following formula.

$$\text{Amount} = \frac{\text{Peak area of sample}}{\text{Peak area of standard}} \times \frac{\text{Standard dilution}}{\text{Sample dilution}} \times \text{Average weight}$$

$$\text{Percentage of drug released} = \frac{\text{Amount}}{\text{Label claim}} \times 100$$

The method is to develop a procedure was carried out in RP – HPLC C18 and the mobile phase conditions were optimized by using different mobile phase ratio at different flow rates. The optimum mobile phase contains Phosphate buffer (pH 6.8): acetonitrile (80:20) and detected at 264 nm (Isosbestic point for both drugs that also confirmed in overlay spectra) using UV/ Visible detector. At 1ml/ min flow rate the method gave a separation at 1.527 min for Metoprolol tartarate and 2.033 min for Atorvastatin calcium in standard.(19,20).

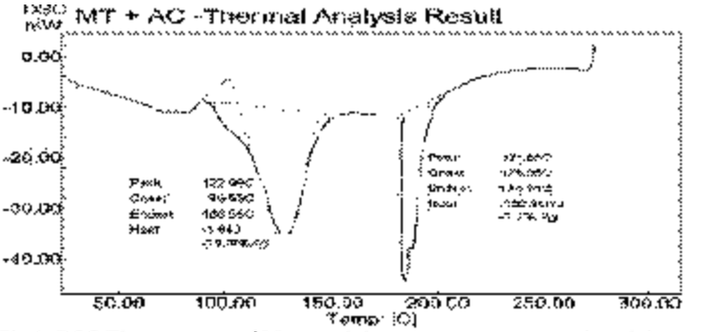

Fig 1: DSC Thermogram of Metoprolol tartarate + atorvastatin calcium

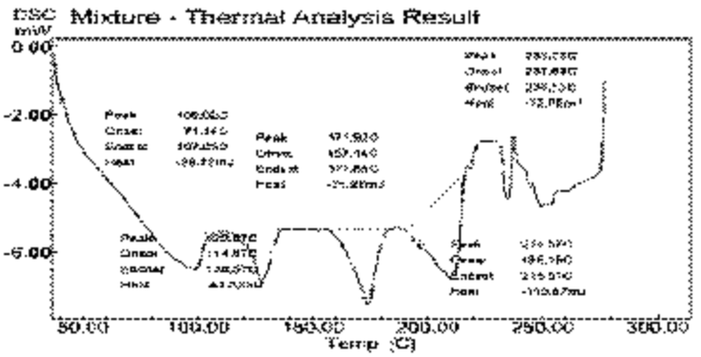

Fig 2: DSC Thermogram of mixture of drugs with polymers and other excipients

Determination of Swelling and Eroding Behavior

Matrix tablet was introduced into the dissolution apparatus under the standard set of conditions as specified for determination of *in vitro* drug release. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were placed in a vacuum oven at 40°C and after 48 hours tablets were removed and weighed. Swelling (%) and Erosion (%) was calculated according to the following formula,

S%=100(H3-H2)/H2

E% =100(H1-H2)/H1

Where, H1=Initial tablet weight: H2 = Dry weight of tablet: H3 = swelled tablet weight

***In vitro* release studies**

The dissolution test for the tablets was carried out by using USP apparatus II, 900ml of 0.1 N HCL and the paddle was rotated at 50 RPM for the first 2 hour. And then 0.1N Hcl was replaced by phosphate buffer of pH 7.4 and the paddle was rotated continuously for upto 24 hours. Samples for immediate release layer were collected at the interval of 0.5,10,15,20,30, 45 and 60 min and for sustained release layer at the interval of 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 & 24 hours. The collected samples were analyzed at 246 nm for Atorvastatin calcium and 274 nm for Metoprolol tartarate by using UV spectrophotometer.(21, 22, 23)

Stability studies

Stability studies were done for tablets for a period of three month (at 40º±2ºC, RH 70±5%).Stability of a pharmaceutical preparation can be defined as the capability of a particular formulation (dosage form or drug product) in a specific container/ closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life.

The accelerated stability study are of great interest and are attractive as satisfactory results can be documented under stressed conditions by which time saving can be achieved. It generates information on which proposal for shelf life of drug or dosage form and their recommended storage conditions are based.(24,25)

Release studies:

Data obtained from *in- vitro* release study were fitted to various kinetic equations.

The kinetic models used were,

- **Zero order equation** : ($Q=k_0 t$)
- **First order equation** : ($\{\ln (100 - Q) = \ln Q - k_1 t\}$)
- **Higuchi equation** : ($Q= kt^{1/2}$)

Further, to find out the mechanism of drug release, first 60% drug release was fitted in Korsmeyer and Peppas equation ($Q = kpt^n$). Where, Q is the percent of the drug release at time 't' and k_0 and kt are the coefficients of the equations and 'n' is the release exponent. The 'n' value was used to characterize different release mechanism.(26, 27, 28)

RESULTS AND DISCUSSION

Once daily dosage form of Inlay tablet of Atorvastatin calcium with sustained release Metoprolol tartarate were formulated using Guar Gum, Eudragit s 100, HPMC K 100 M, and HPMC K 4M.

Compatibility studies:

Compatibility study was accessed by Differential Scanning Colorimeter (DSC).The thermograms have shown an endothermic peak and the results are shown in Fig.1&2. The DSC thermogram indicated that there is no drug – drug interaction and drug – polymer interaction.

Preformulation studies:

The preformulation studies of both Metoprolol tartarate SR and Atorvastatin calcium IR granules were evaluated for various physical properties and the values are shown in the Table 3 & 4. Angle of repose shows that the flow property for both the granules was good and it is within the acceptable limits, less than 35°.bulk density of both the granules indicates good packaging character. The Carr's index for all the formulation was found to be below 15%, which indicate acceptable flow properties. The Hausner's ratio for all the granules was less than 2%.

Table 3: Physical evaluation of Metoprolol tartarate Granules

Formulation	Parameters				
	Angle of repose	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
FM_1	30.46±0.02	0.37±0.01	0.40±0.01	7.35±0.11	1.08±0.01
FM_2	31.21±0.01	0.44±0.01	0.52±0.01	14.28±0.02	1.16±0.02
FM_3	26.48±1.73	0.38±0.01	0.57±0.01	13.05±0.55	1.15±0.01
FM_4	30.48±0.73	0.41±0.01	0.58±0.05	7.86±1.50	1.08±0.01
FM_5	30.48±0.01	0.44±0.02	0.61±0.01	15.18±0.90	1.17±0.01
FM_6	29.80±1.41	0.42±0.01	0.57±0.01	7.60±1.45	1.07±0.02

Table 4: Physical evaluation of Atorvastatin calcium Granules

Formulation	Parameters				
	Angle of repose	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
FA_1	34.18±1.35	0.55±0.05	0.64±0.05	15.36±2.03	1.18±0.03
FA_2	33.60±0.02	0.55±0.03	0.45±0.05	11.35±0.95	1.12±0.01
FA_3	35.53±0.01	0.51±0.01	0.44±0.02	13.25±0.75	1.1±0.06
FA_4	32.85±0.85	0.55±0.05	0.55±0.05	14.12±1.88	1.16±0.03
FA_5	36.17±2.48	0.53±0.01	0.45±0.05	13.81±0.77	1.16±0.01
FA_6	33.76±1.76	0.55±0.05	0.58±0.02	12.10±1.90	1.15±0.05

All the values are mean ± SD of n=3

Assay of the tablets:

The linear methodology shows good reproducibility, the calibration curve was found to be linear. The amount present in the tablet was calculated and the results are shown in Table 5 and Fig 3-4. From the results it was observed that the formulations containing Atorvastatin calcium shows the amount of drug ranges from 100.69 ± 2.34 to 102.34 ± 1.75 % W/V and the formulations containing Metoprolol tartarate shows the amount of drug ranges from 96.38 ± 2.09 to 101.89 ± 2.13 % W/V.

Physical evaluation of Inlay Tablets:

Tablets are selected randomly from all the six batches and physical evaluation of tablets were studied. The table shows the average weight of tablet 0.499 ± 0.04 to 0.505 ± 0.02 mg. The hardness was found to be 6.4 ± 0.2 to 7.8 ± 0.3 kg/ cm^2 and the friability was found to be 0.57 ± 0.04 to 0.28 ± 0.08 %. The thickness of the tablet was found to be 4.92 ± 0.02 to 4.54 ± 0.02 mm. From the above discussion it was found that all the parameters were within the acceptable limits and the results are shown in Table 5.

Table 5: Physical evaluation of Inlay tablet

Parameters	F1	F2	F3	F4	F5	F6
Weight variation (mg)	0.502 ± 0.02	0.499 ± 0.04	0.500 ± 0.02	0.504 ± 0.02	0.502 ± 0.04	0.505 ± 0.02
Hardness kg/cm2	6.6 ± 0.2	7.8 ± 0.3	7.2 ± 0.2	7.6 ± 0.2	7.4 ± 0.2	6.4 ± 0.2
Friability %	0.34 ± 0.14	0.57 ± 0.04	0.47 ± 0.14	0.29 ± 0.02	0.30 ± 0.12	0.28 ± 0.08
Thickness (mm)	4.74 ± 0.02	4.54 ± 0.02	4.92 ± 0.02	4.84 ± 0.02	4.74 ± 0.02	4.74 ± 0.02
Assay %W/W						
Atorvastatin	102.09	100.69	102.05	102.34	102.24	103.28
Metoprolol	100.25	101.89	98.62	100.74	98.56	96.38

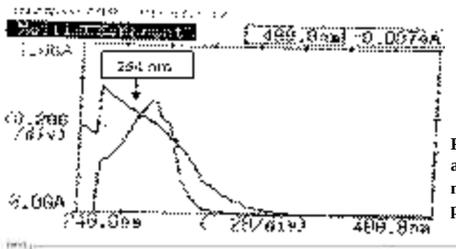

Fig 3 : Overlain spectra of atorvastatin calcium and metoprolol tartarate (isobestic point = 264 nm).

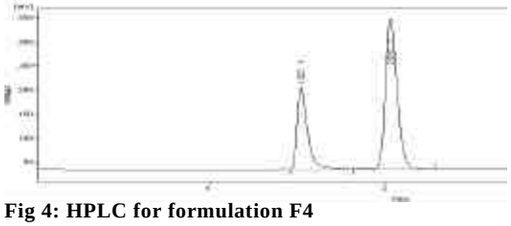

Fig 4: HPLC for formulation F4

Swelling and Erosion studies:

The results of swelling and erosion behaviour of the selected formulation shown in Fig 5. The erosion studies of formulation F4 with guar gum shows increase in swelling percentage with simultaneous decrease in erosion percentage. The result shows that there was a greater swelling and lesser erosion as compared with the other inlay tablets. The release of drug from hydrophilic matrices occurs as a result of complex interaction between diffusion, dissolution, and erosion mechanisms. On coming in contact with phosphate buffer, hydrophilic matrices undergo gel formation.

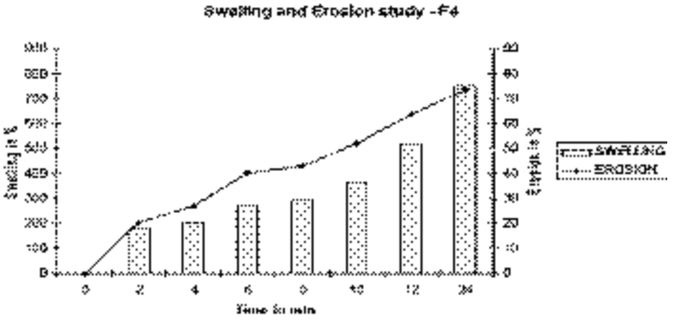

Fig 5: Swelling and Erosion behavior (F4)

***In Vitro* release studies:**

Six different formulations (F1-F6) were prepared and the release characteristics were studied for 24 hrs. Among the six formulations (F1-F6), F4 attained expected release pattern in both immediate release layer (i.e., 99.28% at the end of 20 mins) and in sustained release layer (i.e., 98.42% at the end of 24 hours) and the release pattern of the IR and SR layers shown in Fig 6 & 7.

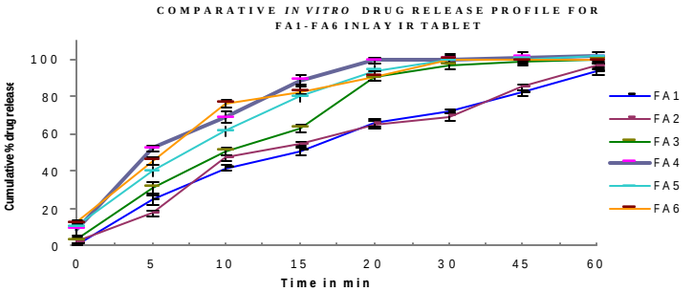

Fig 6: Comparative in vitro drug release profile for FA1-FA6 Inlay tablet (IR Layer)

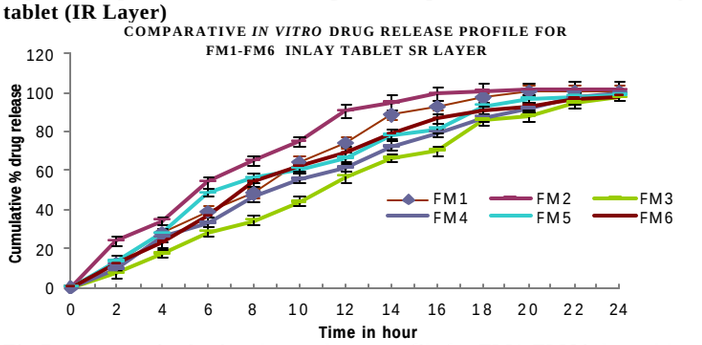

Fig 7: comparative *in vitro* drug release profile for FM1-FM6 inlay tablet (SR Layer).

***In Vitro* release kinetics:**

The *In Vitro* release kinetic studies revealed that the drug release for formulation F4 follows zero order kinetics with release exponent value (n) 0.860 which shows that the mechanism of release of tablet follows Non - Fickian diffusion controlled mechanism (peppas) and the release pattern shown in Table 6 & Fig 8.

Table 6: Release kinetics

Formula code	Drug release kinetics						
	Zero order K_0	r	First order K_1	r	Higuchi r	Peppa's n	r
F4	5.0587	0.9900	0.0730	0.8852	0.9814	0.8870	0.9860

Note: K_0=zero order rate constant, k_1=first order rate constant, r= coefficient of correlation, n=diffusion co efficient.

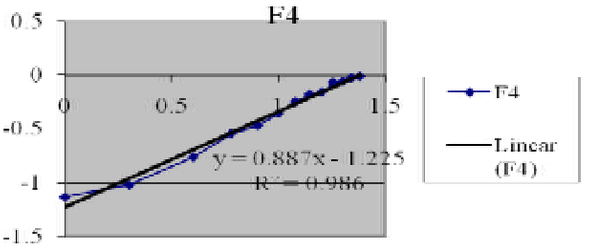

Fig 8: Peppas fitting curve for formulation F4

Table 7: Stability studies of the formulations

Parameter	Duration of Evaluation for formulations													
	F1		F2		F3		F4		F5		F6			
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final		
Appearance	White Smooth	White Smooth	White Smooth	White Ejection of core	White Smooth	White Smooth	White Smooth	White Smooth	White Smooth	White Smooth	White Smooth	White Smooth		
Texture	Within normal limits	No change	Within normal limits	changed	Within normal limits	No change	Within normal limits	No change	Within normal limits	No change	Within normal limits	No change		
Physical properties *														

** Hardness, Weight variation, Thickness, Friability.(All the parameters evaluated for the period of 3 months i.e. 40°±2°C and RH 70±5%)*

Stability studies:

All six formulations, remains stable on storage condition at 40°±2°C and RH 70±5%, with no apparent change in appearance, texture, physical properties, drug content and % drug release, except F2 which shows a small ejection of Inlay tablet and the results are shown in Table 7.

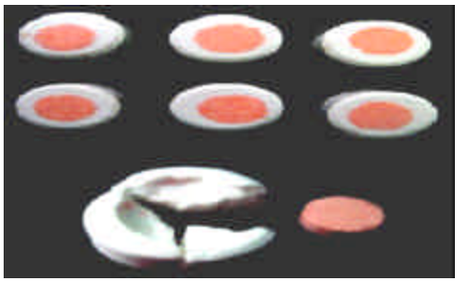

Fig 9: Inlay Tablet

Fig 10: Release Pattern of Inlay Tablets, ejection of inner core tablet followed by disintegration of IR and swelling of SR

CONCLUSION:

Inlay tablet is a novel technology which overcomes the difficulties that faced in other compression coated tablets. The formulation F4 has achieved the objective of controlled drug delivery with prolonged drug release, cost effective, low dose and frequency of administration and hence improved patient compliance. Thus it may concluded that the once daily Inlay tablet of Atorvastatin calcium with sustained release Metoprolol tartarate can be a best alternate to conventional dosage forms with more frequency of administration. The Inlay tablet can be administered to patients with Hypertension and Dyslipidemia, Myocardial infarction, Diabetic dyslipidemia and Hypertension.

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