

Formulation Development and *in vitro* - *in vivo* studies on Colon Targeted Oral Delivery System of Atorvastatin

Sivakumar Kalidoss^{1*} and Kailasam Koumaravelou²

¹ Centre for Research & Development, PRIST University, Thanjavur

² Director, PRIST University, Puducherry

Abstract:

The aim of the present work was to development of colon targeted delivery system of atorvastatin and evaluate *in vivo* and *in vitro* studies performed for the formulated tablets. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different polymers. Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. Drug and physical mixture were evaluated for compatibility study by DSC. All the batches of matrix tablet (ACD1-ACD5) were subjected for *in-vitro* dissolution in various simulated gastric fluids for suitability for colon specific drug delivery system. The amount of atorvastatin released from tablets at different time intervals was estimated by RP-HPLC methods. Among all the formulations ACD5 formulation was found to be optimized as it was retarded the drug release up to 24 hours and showed maximum of 99.13 % drug release. The diffusion mechanism of drug release was further confirmed by Korsmeyer – Peppas plots that showed good linearity (R^2 values between 0.97 and 0.99), with slope > 0.5, indicating that drug release mechanism from the formulations were Fickian diffusion mechanism. The relative bioavailability (RB) was also found to be high and thus it indicates that atorvastatin released more amounts from the CTDD tablet formulation and absorbed for blood circulation with an acceptable plasma concentration. The studies confirmed that, the designed formulation could be used potentially for colon delivery by controlling drug release in stomach and the small intestine.

Key words: Atorvastatin, Colon targeted drug delivery system, *in vitro* dissolution, *in vivo* studies.

INTRODUCTION

In recent years, colon targeted delivery systems have been the focus point of formulation laboratories because the colon¹ is considered as a suitable site for delivery of both conventional and labile molecules, and it is also a site for some specific diseases, such as, ulcerative colitis, Crohn's disease bowel cancer, some infections². The most critical challenge in such drug delivery approach is to preserve the formulation during its gastric transit time as well as the length of the small intestine. In order to develop a reliable colonic drug delivery system, the transit time of dosage forms through the gastrointestinal (GI) tract needs to be understood well^{3,4}. The transit of perorally administered formulation through the GI tract is highly variable and depends on various factors. For example factors like disease state of the lumen (diarrhea, diabetes, peptic ulcer etc)⁵, concomitant administration of other drugs (domperidone, cisapride, metoclopramide etc), body posture (vertical or supine) and food type (fat and protein content) can influence the gastric emptying rate. Gastric transit time of single-unit non-disintegrating dosage forms is highly variable between 15 mins to 3 hours^{6,7}. There are various methods or techniques by which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH-sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure controlled drug delivery systems, osmotic pressure controlled systems⁸.

Atorvastatin is a synthetic lipid-lowering agent, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Atorvastatin undergoes rapid oral absorption, with an approximate time to maximum plasma concentration (T_{max}) of 1–2 hours. The absolute bioavailability of the drug is approximately 14%; however, the systemic availability for HMG-CoA reductase activity is approximately 30%. Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability. The objective of the present study was to develop a controlled release colon targeted drug delivery system of Atorvastatin for the treatment of anti lipidemic agents.

MATERIALS AND METHOD

Materials

Atorvastatin was provided as a gift sample by Cadila Ltd, (Ahmedabad, India). Eudragit L 100 D 55, Eudragit S 100 and Shellac were purchased from Loba chemicals, Mumbai. Other materials used in the study namely, Calcium carbonate, Lactose mono hydrate, micro crystalline cellulose (Avicel PH 101), aerosil, talc and Magnesium stearate were of pharmacopoeial grade. All the other chemicals were of analytical grade. A tissue tearer (BioSpec Products, Inc., USA) and ultrasonic cell disruptor- Branson Ultrasonics™ Sonifier S-250A Analog Ultrasonic Cell Disruptor/Homogenizer (Branson Ultrasonics™, USA) were used for tissue homogenization. After sterilization surgical equipments/instruments such as scissors, forceps, glass syringes, etc. were utilized to during the study.

Methods

Formulation of Atorvastatin tablet

Atorvastatin Tablets was prepared by the wet granulation technique using 10% w/v starch paste. The compositions of different matrix tablet formulation used in the study containing ACD are shown in Table 1. The powders (F1-F5) were blended and granulated with 10% w/v starch paste. The obtained wet mass was pass through sieve number 16 (mesh size: 1000 μm) and the granules were dried at 50° C for 2h. The dried granules were pass through sieve no. 25 (mesh size: 650 μm) and were lubricated with mixture of talc and magnesium stearate in definite proportion. The lubricated granules were compressed in to the tablets with the target weight 175mg, using 7mm standard concave punches. Cadmach Mini Rotary Tablet Press 9 station, multi tooling was used for tablet punching. (Cadmach Machinery Co Pvt. Ltd)

Step – II

The optimized formulation of tablet was coated using a combination of Eudragit L 100 and S100 by using a fluidized bed coating apparatus. Coating solution was prepared by dissolution of 500 mg of Eudragit polymers (L-100 and S-100; 1:1) in ethanol: acetone (2:1) to give 10% coating. PEG 4000 (1% w/v) was used as a plasticizer. Coating solution was applied until there is no drug release in simulated gastric fluid. A 10% w/w increase in the

coating level was selected as an optimum coating percentage level⁹.

Table 1: Composition of Tablet formulations

Ingredients(mgs)	ACD-1	ACD-2	ACD-3	ACD-4	ACD-5
Atorvastatin calcium	10.00	10.00	10.00	10.00	10.00
Ethyl cellulose	10.00	20.00	30.00	40.00	50.00
Calcium carbonate	35.00	25.00	25.00	25.00	25.00
Microcrystalline cellulose	37.00	42.00	37.00	32.00	32.00
Lactose Mono hydrate	73.00	63.00	63.00	58.00	48.00
Croscarmellose sodium	5.00	5.00	5.00	5.00	5.00
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	3.00	3.00	3.00	3.00	3.00
Magnesium Stearate	2.00	2.00	2.00	2.00	2.00
Core Tablet weight (mg)	175.0 0	175.0 0	175.0 0	175.0 0	175.0

Preformulation studies

Differential scanning calorimetry studies

Differential Scanning Calorimetry (DSC) was performed to study the physical and chemical interaction between the drug and excipients that were used. DSC thermogram of pure drug and drug composite mixture were recorded on DSC-METTLER STAR SW-9.20 instrument. The drug-excipient mixture was scanned in the temperature range of 50-400 °C under the atmosphere of nitrogen. Aluminium pans and lids were used for all samples. The heating rate was 20 °C/min and the obtained thermograms were observed for any type of interaction.

Evaluation Of Tablets

Tablet thickness

Thickness was measured using a calibrated screw gauge. Three tablets of each formulation were picked randomly and thickness was measured individually.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets was determined.

Friability

Friability of tablets was determined using Roche friabilator. Twenty tablets were weighed and placed in a chamber. The friabilator was operated at 25 rpm for four minutes (per 100 revolutions) and the tablets were subjected and the tablets were subjected for combined effect of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution¹⁰. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula,

$$F = \frac{W_i - W_f}{W_i} \times 100$$

Weight variation

Weight variation test was performed according to USP 2004, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The percentage deviation was calculated and checked for weight variation¹¹.

In - Vitro Dissolution Studies¹²

The release rate of atorvastatin colon specific tablets were determined using USP dissolution testing apparatus I (basket type). The test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5°C and 100 rpm for first 2 h. then replaced with 6.8 pH phosphate buffer and continued for 24 h. Aliquot volume of 5 ml was withdrawn at regular intervals and replaced with fresh buffer

diluted. The samples were replaced with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug.

Kinetic Modelling Of Drug Release Profile

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time)¹³ (Higuchi *et al.*, 1963), Hixson-Crowell model¹⁴ and Korsmeyer-Peppas¹⁵ (log cumulative percentage of drug released versus log time) equation models for analyzing the mechanism of drug release and release kinetics from the dosage form using Microsoft Excel 2007. The model with the highest correlation coefficient was considered to be the best fitting one¹⁶.

Pharmacokinetic Studies Of Atorvastatin Pure And Selected Formulation

Animals

Healthy either gender rabbits were selected and conducted pharmacokinetic studies for the selected formulations of Atorvastatin (ACD5) in plasma. Rabbits having 2±0.35 kg of body weight were selected for the study. Animals were fed with standard pellet diet and water *ad libitum*. The selected rabbits were housed in controlled temperature with humidity as well as artificial light and dark cycles (12h) before starting experiment. The selected rabbits were fasted overnight prior to study and water was provided. All experimental protocols were approved by the Institutional Animal Ethics Committee (PRRM College of Pharmacy, Utukur, Kadapa, India.(As per the ref no. CPCSEA/COP/12/04-12-2015) and experiments were conduct in accordance with Committee for the Purpose of Control and Supervision of

Experiments on Animals (CPCSEA).

Group I : Pure atorvastatin (0.6 mg/day)

Group II : Selected formulation ACD5 (Atorvastatin 0.6 mg)

Pharmacokinetic Analysis

Single dose oral administration of CTDD was made for the studies. The drug concentration levels in plasma was determined at different time intervals. The objective of this study was to find the drug disposition of the selected drug after administration. For the three selected CTDD formulations Atorvastatin (ACD5), the following pharmacokinetic parameters were calculated/ measured:

- C_{max} (µg/ml) was determined from the plasma concentration versus time graph.
- T_{max} (hr) was determined from the plasma concentration versus time graph.
- Elimination rate constant (K_{el} , hr⁻¹) was calculated by least-squares regression method.
- $t_{1/2 e}$ (hr) was calculated from the equation: $t_{1/2} = 0.693/K_{el}$.
- Absorption rate constant (K_a , hr⁻¹) and absorption half-life ($t_{1/2 a}$, hr) were determined by using the method of residuals.
- The area under the plasma concentration versus time curve (AUC (0-t), µg.h/ml) and the area under the first moment curve (AUMC (0-t), µg.h/ml) from 0 to 24 hours were calculated from the linear trapezoidal method.
- Area Under the Plasma Concentration versus Time curve (AUC (0-∞), µg.h/ml).
- Area Under the First Moment Curve (AUMC (0-∞), µg.h/ml).
- Mean Residence Time was (MRT (0-∞), hr) from 0 to infinity.
- Volume of distribution (V_d , L).
- Clearance (Cl , L.hr⁻¹)
- Relative bioavailability (RB)

The parameters were calculated using following equations 17,18,19,20,21

$$\text{AUC (0-}\alpha\text{)} = \text{AUC (0-t)} + \text{Fpt/Kel}$$

$$\text{AUMC (0-}\alpha\text{)} = \text{AUMC (0-t)} + \text{Fpt / Kel} + \text{Fpt/Kel}^2$$

$$\text{MRT (0-}\alpha\text{)} = \text{AUMC/AUC}$$

$$\text{Cl} = \text{Dose/AUC}$$

$$\text{Vd} = \text{KaFX}_0 / \text{Log A (Ka-Ke)}$$

$$\text{RB} = \text{AUC (0-t) (test) / AUC (0-t) (reference)} \times 100\%$$

Where Fpt = Final drug concentration in plasma at time t

$$\text{Kel} = \text{Elimination rate constant;}$$

$$\text{F} = \text{Fraction of drug absorbed}$$

$$\text{X}_0 = \text{Dose administered at starting;}$$

$$\text{RB} = \text{Relative Bioavailability}$$

$$\text{Log A} = \text{Y-intercept of the last portion of the plot (i.e log extrapolated drug concentration in plasma vs time curve)}$$

$$\text{AUC o-t (test)} = \text{Area under plasma concentration versus time curve from 0 to 24 hours for all the three selected formulations}$$

$$\text{AUCo-t (reference)} = \text{Area under plasma concentration versus time curve from 0 to 24 hours of pure suspension of all three drugs}$$

Analysis of Biological Samples

The pharmacokinetic parameters study, after oral administration of the selected formulations, ACD5(Atorvastatin 0.6mg) CTDD tablets and pure drug of Atorvastatin tablets respective group of animals. Blood samples (0.2 mL) were withdrawn from the marginal ear vein of rabbits at scheduled time intervals (0, 2, 4, 8, 12, 16, 20, 24, 26 and 30 hours) and collected into heparinized tubes. From the samples of plasma and blood obtained was centrifuged at 12000 rpm for 10 minutes at -40°C , which was then preserved in glass tubes and frozen at $-25^{\circ}\text{C} \pm 2.0$.

To 0.5 mL of plasma and tissue samples, 0.2 mL mobile phase, 0.1 mL of 5% v/v formic acid was added and the drug was eluted by methanol by using solid phase extraction. The eluates were evaporated to dryness at 40°C under Nitrogen gas. Residues were then reconstituted in 0.5 mL of mobile phase.

Pharmacokinetic Data analysis

By using The MathWorks, Inc. V2 Demo software non-compartmental analysis was performed for the drug concentration in various tissues and plasma at different time period. Pharmacokinetic parameters like C_{max} , V_d , K_e , $t_{1/2}$, Cl , $\text{AUC}_{0-\infty}$ and MRT were calculated for selected, ACD5 formulations. The results of the *in-vivo* pharmacokinetics parameters for selected formulations were measured using suitable statistical tests with $P < 0.05$ level of significance.

RESULTS AND DISCUSSION

Differential scanning calorimetry studies

Thermograms were obtained for pure Atorvastatin and mixed matrix containing Atorvastatin with other excipients. Pure

powdered Atorvastatin showed a melting endotherm at 164°C , found in Figure 1. There was no significant difference in the melting point of drug in both samples. It indicates that the drug was present in its characteristic physical and chemical form. It was compatible with all the excipients present in the tablet and there was no major interaction of the drug with the excipients which were presented in Figures 1 to 3.

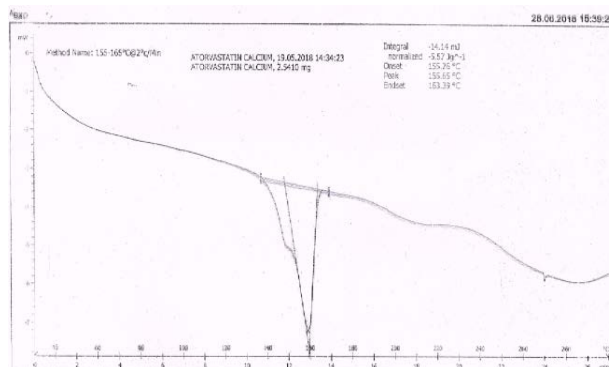


Figure 1: DSC spectrum of Atorvastatin API

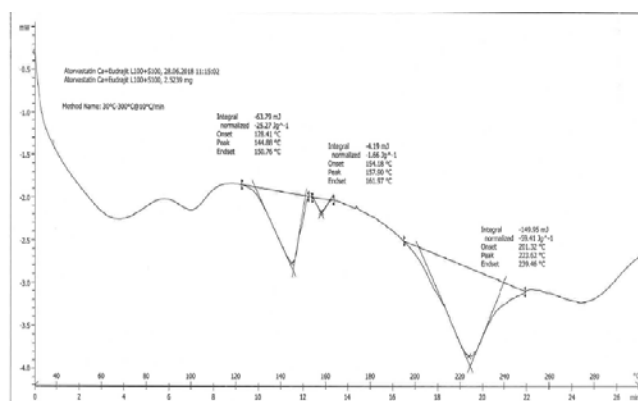


Figure 2: DSC spectrum of Atorvastatin calcium + Eudragit (L-100 and S-100)

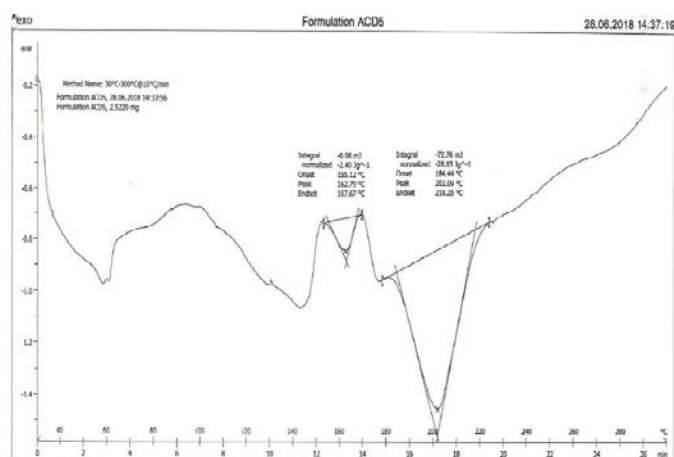


Figure 3: DSC spectrum of Atorvastatin formulation ACD 5

Evaluation of atorvastatin colon targeted tablets

The physical properties of colon targeted tablet of atorvastatin was presented in the table 2. Tablets were also evaluated for the hardness using hardness tester (Schleuniger), friability using a Roche friability apparatus (Electrolab, India) and thickness using digital vernier calipers. The thickness of tablets was found to be between 6.42-6.55 mm. The hardness for different formulations was found to be between 4.6 to 5.4 kg/cm², indicating satisfactory mechanical strength. The friability and weight variation uncoated

tablets of different tablet formulations were found in compendial limits, i.e. 0.44 ± 0.043 to 0.57 ± 0.054 and 175.22 ± 0.45 to 175.82 ± 0.22 respectively, which is an indication of good mechanical resistance of the tablet. Drug content was found to be in the range of 99.13 ± 0.67 to 100.24 ± 0.67 % which is within acceptable limits.

IN VITRO DRUG RELEASE STUDIES

The release of atorvastatin from colon targeted tablets varied according to the types and proportion of polymers content in the various formulations. The results of cumulative drug release of CTTDS formulations from ACD1 to ACD5 are shown in table 3 and Figure 4. CTTDS tablets from ACD2 to ACD5 released 98.66%, 98.45%, 98.37% and 99.79% respectively, of their atorvastatin content at the end of 24 hours. The values are expressed in terms average of three dissolution profile. All four values of drug release percentage at 24 hours in the different batches differed significantly (single factor ANOVA) at $P < 0.001$ (DF=2, F=15.04). CTTDS Formulations of atorvastatin from ACD1 to ACD5, containing ethyl cellulose and coated in combination with Eudragit L 100 along Eduragit S 100,

successfully released $< 90\%$ at the end of 20 hours. Formulations were impermeable, may be due to reduced water penetration in the matrix. At the end of 2 hours drug released from ACD1 to ACD5 were 16.23%, 13.12%, 11.42%, 9.12% and 5.34% whereas at the end of 24 h drug release from ACD2 to ACD5 was found to be 98.66%, 98.37%, 98.37% and 99.13%, respectively. Formulation ACD1 was failed to release requirements $> 90\%$ at the end of 24 hours. The differences between 16 hours release values for ACD2, ACD3, ACD4 and ACD5 were significant at $P < 0.01$ (DF=2, F= 99). Significant differences were observed between 24 hours release values ($P < 0.01$, DF=2 and F=90). Incorporation of higher amount of ethyl cellulose in all the four formulations (ACD2, ACD3, ACD4 and ACD5) was found to be more suitable to give good drug release characteristics and ACD5 was found to have a good release profile. As the concentration of ethyl cellulose increases retardation nature also increased. The duration of drug release was slower with formulation ACD5 which was about only 99.13 % in 24 h from among the formulations ACD1 to ACD5.

Table-2 Physicochemical parameters of developed colon targeted tablets of Atorvastatin

Parameters	ACD-1	ACD-2	ACD-3	ACD-4	ACD-5
Hardness Kg/cm ²	5.4 ± 0.35	5.2 ± 0.42	5.2 ± 0.32	5.0 ± 0.42	4.6 ± 0.28
Friability % loss	0.57 ± 0.054	0.54 ± 0.068	0.47 ± 0.022	0.48 ± 0.024	0.44 ± 0.043
Thickness mm	6.50 ± 0.032	6.44 ± 0.043	6.44 ± 0.034	6.53 ± 0.022	6.42 ± 0.042
Weight variation -Core tablets (mgs)	175.82 ± 0.22	175.42 ± 0.27	175.44 ± 0.43	175.34 ± 0.34	175.22 ± 0.45
Weight Variation of coated tablets (mg)	180.42 ± 0.34	180.56 ± 0.32	180.76 ± 0.45	180.87 ± 0.46	180.22 ± 0.22
Drug content (%)	99.13 ± 0.67	99.66 ± 0.88	99.71 ± 0.92	99.72 ± 0.22	100.24 ± 0.26

Table-3 In vitro drug release study of different formulation of Atorvastatin colon targeted Tablets

Dissolution Media	Time (Hrs)	Formulations (cumulative percentage drug release)				
		ACD-1	ACD-2	ACD-3	ACD-4	ACD-5
Simulated gastric fluid	2	16.23	13.12	11.42	9.12	5
Simulated intestinal fluid	4	51.88	32.12	25.25	20.76	14.12
Simulated colonic fluid	8	80.22	77.34	61.41	38.18	28.76
	12	96.14	83.89	79.60	60.34	54.34
	16	99.76	93.12	93.44	79.87	72.98
	20	-	98.24	97.08	94.33	90.65
	24	-	98.66	98.37	98.37	99.13

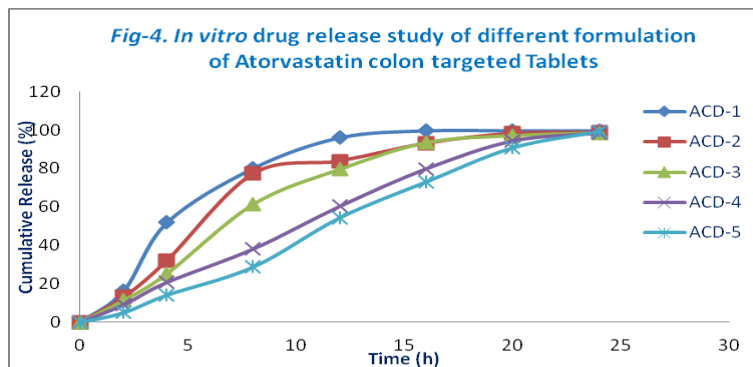


Table 4 In-vitro release kinetics for proposed formulation (ACD1 to ACD5) of Atorvastatin colon targeted Tablets

Formulation	Zero order	First order	Hixson-Crowell	Higuchi	Koresmeyars -Pappas	
	R ² Value	R ² Value	R ² Value	R ² Value	R ² Value	'n' Value
ACD1	0.676	0.932	0.732	0.276	0.890	0.371
ACD2	0.795	0.973	0.967	0.878	0.973	0.295
ACD3	0.872	0.974	0.979	0.897	0.990	0.309
ACD4	0.977	0.902	0.966	0.804	0.893	0.288
ACD5	0.989	0.999	0.932	0.889	0.998	0.302

IN VITRO RELEASE KINETIC FOR THE FORMULATION (ACD1 TO ACD5) OF ATORVASTATIN.

The dissolution data (from the values of 2 to 24 hours of release of drug) of all formulations were fitted to first-order, Higuchi, zero-order and Korsmeyer – Peppas models. The formulations didn't follow zero-order release kinetics. Correlation coefficient (R^2) was calculated to find the best fitted model for drug release and their values are provided in the table no 4. While the data were plotted in graph according to a first-order of reaction equation, the formulations from ACD2 to ACD5 have shown a good linearity to their regression values 0.973, 0.974, 0.902 and 0.999, respectively. The best fit with higher correlation ($R^2 > 0.87$) was found with the Korsmeyer – Peppas for ACD2, ACD3 and ACD5 CTTDS tablets. Drug release from a hydrophobic matrix tablets involved in pore diffusion and matrix erosion. Dissolution resulted in complete release of drug, may be the coating of certain fraction of drug by ethyl cellulose and coated in combination with Eudragit L 100 along Eduragit S 100. The release profiles of ACD2, ACD3 and ACD5 might be well clarified by Higuchi model, as the plots showed good linearity and correlation coefficient (R^2) values 0.878, 0.897 and 0.889 respectively. The diffusion mechanism of drug release was further confirmed by Korsmeyer – Peppas plots that showed good linearity (R^2 values between 0.97 and 0.99), with slope > 0.5 , indicating that drug release mechanism from the formulations were Fickian diffusion mechanism^{22,23}

In Vivo Pharmacokinetic Studies

Oral Route of Administration Conventional Atorvastatin Tablet (ACD) and Selected Formulation (ACD5) of CTDD Tablet

The mean pharmacokinetic parameters and the plasma drug concentrations vs time profile curve following oral administration of 60 µg of atorvastatin for the (i) conventional atorvastatin tablet (ACD) and (ii) selected formulation (ACD5) of colon targeted drug tablet after oral administration in six rabbits for each batch are shown in Table 5 and 6 and graphically represented in Figure 5 and 6 respectively. It was found that for the colon targeted drug tablet formulation. The C_{max} was not decreased significantly but T_{max} was delayed significantly when compared with the conventional tablet. Moreover, the curve also shows that in the initial hours, the plasma concentration of atorvastatin was reduced. The relative bioavailability was found to be high. Thus, it is confirmed that the maximum amount of atorvastatin was released from the selected formulation of CTDD in the colonic region. In 95 % confidence interval, parameters like k_e , V_d , Cl , $t_{1/2}$, $AUC(0-\infty)$, $AUMC(0-\infty)$, MRT (hrs) and relative bioavailability of the selected formulation (ACD5) was significantly ($P < 0.005$) improved when compared with conventional atorvastatin tablet.

Table 5 Plasma Drug Concentration Vs Time Profile for the atorvastatin drug ACD and selected formulation ACD5

Time (Hrs)	ACD	ACD5
0	0	0
2	14.64	9.18
4	45.12	23.1
8	6.36	27.54
12	-	36.06
16	-	45.36
20	-	51.3
24	-	57.24
26	-	19.26
30	-	9.72

Table.6. Mean pharmacokinetic parameters for the atorvastatin drug ACD and selected formulation ACD5

Pharmacokinetic Parameters	ACD	ACD5	P – Value
C_{max} (µg)	45.12 ± 1.63	45.36 ± 1.29	NS
T_{max} (hrs)	4 ± 0.52	16 ± 0.44	< 0.005
k (hr^{-1})	0.19 ± 0.09	0.09 ± 0.001	
V_d (L)	1.75 ± 0.72	0.69 ± 0.08	
Cl (L/hr)	0.33 ± 0.02	0.06 ± 0.001	
$t_{1/2}$ (hrs)	3.66 ± 0.81	7.87 ± 1.07	
$AUC(0-\infty)$ (µg.hr/ mL)	181.61 ± 11.33	994.00 ± 22.39	
$AUMC(0-\infty)$ (µg ² .h ² /ml)	59.76 ± 1.84	32.28 ± 1.85	
MRT (hrs)	0.33 ± 0.09	0.03 ± 0.001	
Relative Bioavailability (%)	30.55 ± 2.61	86.18 ± 3.89	

NS = Not Significant

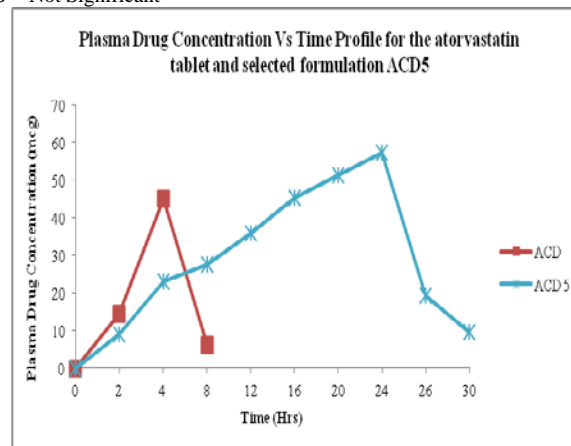


Figure.5. Plasma Drug Concentration Vs Time Profile for the atorvastatin tablet and selected formulation ACD5

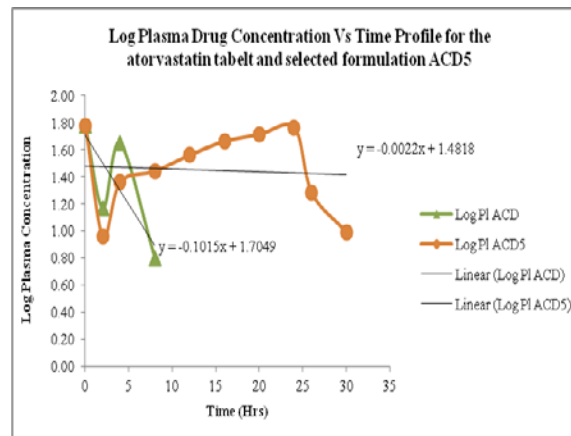


Figure.6. Log Plasma Drug Concentration Vs Time Profile for the atorvastatin tablet and selected formulation ACD5

The pharmacokinetic parameters of the colon targeted drug delivery tablet formulation of atorvastatin as a novel drug delivery system and also to calculate the relative bioavailability in terms of percentage. Pharmacokinetic analysis results showed a clear and significant difference among the conventional and CTDD tablet formulations. In the CTDD tablet formulation, the C_{max} was almost similar (no significant changes) with improved T_{max} when compared with conventional tablet dosage form of atorvastatin. Additionally, the curve shows that at the early time periods, the plasma concentration of atorvastatin was less because of the presence of polymer the Ethyl cellulose has pH-dependent solubility which retards the release of atorvastatin throughout the gastro intestines of rabbits. The release of atorvastatin was improved in the colonic region of rabbits and hence there was a

high plasma concentration of atorvastatin which is because of the high solubility of ethyl cellulose polymer in the colonic pH. This reduced C_{max} initially and at T_{max} was delayed and lower plasma concentration of atorvastatin in the early hours from the colonic targeted drug delivery tablet formulation in comparison with the conventional tablet shows that the atorvastatin was only targeted in the colonic region and was not released in the gastro intestinal tract.

The CTDD tablet formulation was also characterized by a reduction in the elimination rate (k_e) constant and an increase in the half-life (t_{1/2}) compared to the conventional atorvastatin tablet. The results clearly indicate the flip-flop phenomenon which is in-line as stated in the literature (Schall, R, et al 1992), which is one of the associations either with sustained and/ or delayed release formulations. Another indication of delayed delivery of atorvastatin from the CTDD tablet formulation is a slower rate of absorption C_{max}/ AUC(0-∞) and a maximum mean residence time (MRT) when compared with the conventional atorvastatin tablet. The volume of distribution (V_d) was maximum and delayed clearance (Cl) from the CTDD tablet formulation, suggesting that the improve in mean residence time was because of delayed absorption of atorvastatin.

Furthermore, the relative bioavailability (RB) was also found to be high and thus it indicates that atorvastatin released more amounts from the CTDD tablet formulation and absorbed for blood circulation with an acceptable plasma concentration.

CONCLUSION

The present investigation was concerned with the development of the colon targeted tablets, which after oral administration were designed to prevent the drug release in stomach and small intestine. It improves the bioavailability of the drug as well as its half life. The invitro dissolution results generated in the pharmaceutical laboratory and in vivo bioavailability data generated in the animal studies. Drug release studies shows that ACD5 shows good release behavior in colon and restricts release in stomach and intestine as compare to ACD1 to ACD5. the relative bioavailability (RB) was also found to be high and thus it indicates that atorvastatin released more amounts from the CTDD tablet formulation and absorbed for blood circulation with an acceptable plasma concentration. From the above investigation it was observed that formulation ACD5 was found to be best among the prepared formulations for *invitro* and *invivo* bioavailability studies, which may be used for prolong drug release in colon for, thereby improving patient compliance and bioavailability.

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