Formulation and Evaluation of Solubility Modulated Atorvastatin Calcium as Colon Specific Drug Delivery

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***Abstract*: Hyperlipidemia or hyperlipoprotienemia or dyslipidemia is the presence of elevated or abnormal levels of lipids or lipoproteins in the blood.Lipid and lipoprotein abnormalities are regarded as a highly modifiable risk factor for cardiovascular diseases due to influence of cholesterol.**

Statins are the most commonly prescribed lipid-lowering agents because they are effective ,well tolerated and easy to administer. Atorvastatin is a selective competitive inhibitor of HMG CoA reductase.Its absolute bio availability is 14%.Atorvastatin is slightly soluble in water,BCS Class II drug. Based on Atorvastatin calcium characteristics the bioavailability is improved by complexation technique with β-Cyclo dextrin a solubilizing agent by solvent evaporation method.

After these the coating is done with methacrylic acid copolymers for the targeting action to avoid first pass metabolism and convertion of Atorvastatin calcium into its respective lactone. This project theme is to lowering the cholesterol level by using statins drug of Atorvastatin calcium and it is unstable in gastric pH, so it is targeted to colonic pH which is stable and less side effects.

***Keywords*: Atorvastatin Calcium , β-Cyclo dextrin, HMG CoA, Colon Specific.**

Introduction

The colon is a site where both local and systemic delivery of drugs can take place. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the gastric intestinal tract (GIT) and then to be ensured abrupt or controlled release in the proximal colon.

Advantages of CDDS over conventional drug delivery

- Targeted drug delivery can be achieved.
- Dose of the drug administered can be decreased
- Side effects are less
- It is a promising site for a drug which is unstable or poorly absorbed from upper GIT.
- Targeting to colon can be prevent interaction with the healthy or diseased gut by drugs and excipients.

Atorvastatin undergoes rapid oral absorption, with an approximate time to maximum plasma concentration (Tmax) 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 commonly used approaches for colon targeting are

- pH dependent
- Time dependent
- Pressure dependent
- Bacteria dependent

Cyclo dextrins:

Cyclodextrins result from the cyclomaltodextrin glucanotransferase (E.C. 2.4.1.19; CGTase) catalyzed degradation of starch. They form soluble inclusion compounds with less-hydrophilic molecules that fit into their cavities. here are three common cyclodextrins with 6, 7 or 8 D-glucopyranonsyl residues (α-, β-, and γ-cyclodextrin respectively) linked in a ring by α-1,4 glycosidic bonds. The glucose residues have the 4C1 (chair) conformation. The cavities have different diameters dependent on the number of glucose units (empty diameters between anomeric oxygen atoms given in the diagram below). The side rim depth (shown below in the diagrams) is the same for all three (at about 0.8 nm). γ-Cyclodextrin is most flexible and easily hydrolyzed

by α-amylases whereas α-cyclodextrin is most rigid and only very poorly hydrolyzed. The cyclodextrins, by themselves, are natural, non-toxic additives. The hydroxyl groups may be derivatized to modify the specificity, physical and chemical properties of the cyclodextrins. The 6-OH groups are most easily derivatized.

The absorption of compound from colon is affected by residence in any particular segment of the colon.The transit time in the small intestine is relatively constant than stomach and colon.When dosage forms reach the colon transit depend upon the size of the particle.

Table 1: Average pH in the GIT:

Location	pH
Oral cavity	6.2-7.4
Oesophagus	5.0-6.0
Stomach	Fasted condition : 1.5-2.0 Fed condition :3.0-5.0
Small intestine	Jejunum:5.0-6.5 Ileum;6.0-7.5
Largr intestine	Right colon:6.4 Mild colon and left colon:6-7.6

Table 2: Anatomical and physiological featue of small intestine and colon:

S.no	GIT segment	length	Surface area (m2)	Micro organisms	Transit time
1	Stomach	0.2	0.1	$\leq 10^2$	Variable
2	Small intestine				
	Duodenum	0.3	0.1	≤10	2hr
	Jejunum	3	6.0	≤10	1.5hr
	Ileum	4	6.0	≤10	1.5hr
3	Large intestine	1.5	0.3	≤10	≤48hr

Literature review:

Sivakumar kalidoss et.al (IJCPS, 2016) Atorvastatin colon targeted different formulations were developed by using release rate controlling Research Article www.ijcps.com 6 polymers like Ethyl cellulose by wet granulation methods and then the tablets were enteric coated with Eudragit polymers (L-100 and S-100; 1:1) polymers.

Anil K. Philip et.al (Oman Med J,2010) The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems

Palem CR et.al (PDA J Pharm Sci Technol,2009) The phase solubility profile indicated that the solubility of ATN Ca was significantly increased in the presence of beta-CD and was classified as AL-type, indicating the 1:1 stoichiometric inclusion complexes. Solid complexes prepared by physical mixing, kneading, co-evaporation, and freeze-drying methods were characterized using differential scanning calorimetry, fourier transform infrared spectroscopy, and powder X-ray diffractometry.

The primary intent of the present study was to increase the solubility of Atorvastatin Calcium by forming complexation with β-cyclo dextrin.

The secondary intent was to design and develop the colon specific delivery systems of Atorvastatin Calcium tablets that could be formulated by application of the coating technics ,and by using pH sensitive polymers like Eudragit L100 and Eudragit S100.

The tertiary intent was to evaluate the formulated tablets of Atorvastatin Calcium for its physical characteristics and invitro release profile in stimulated gastric fluid , stimulated intestinal fluid and stimulated colonic fluid.

Finally the colon targeting activity of the above polymers as in combination or individual was studied indetailed.

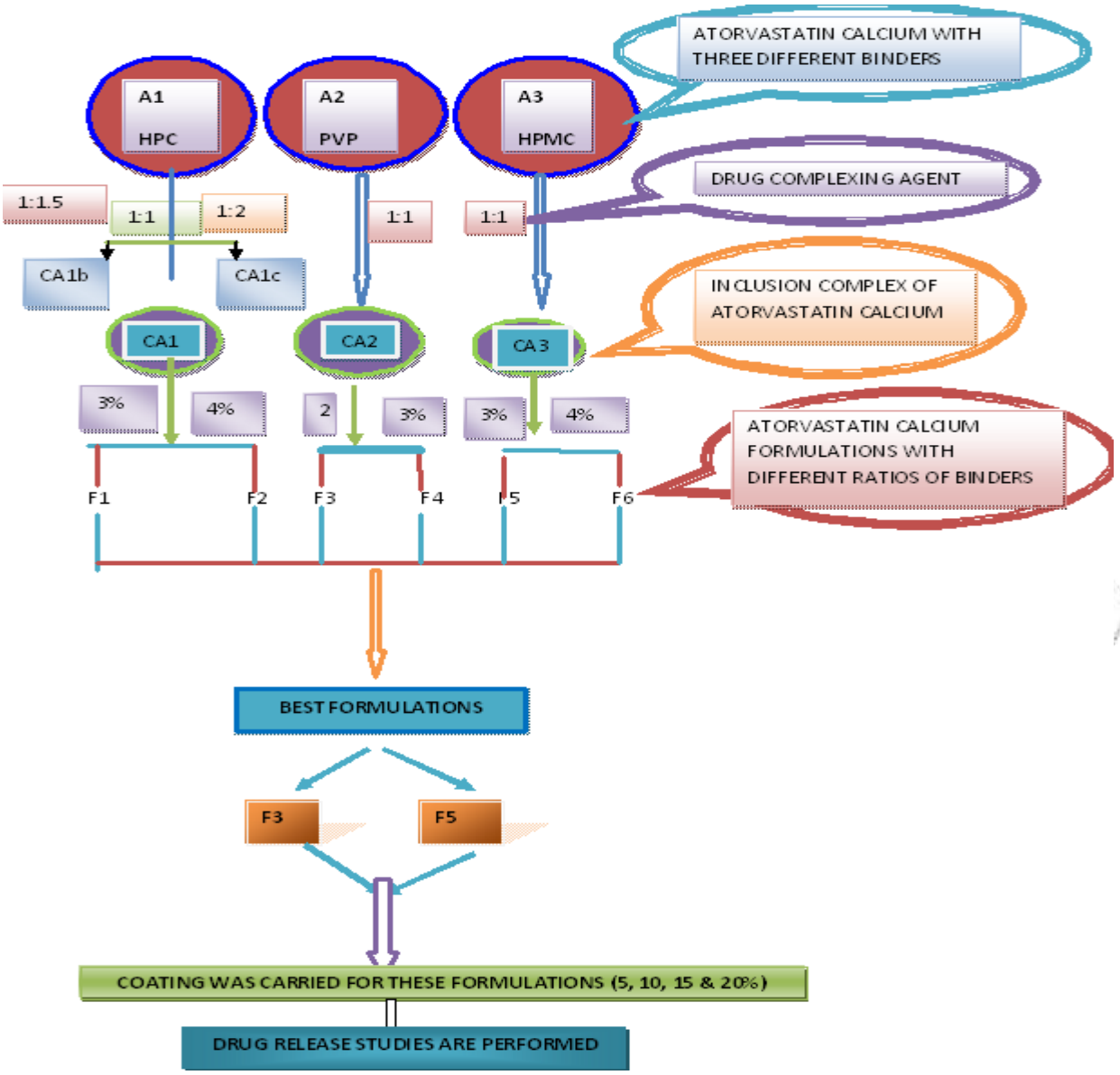
The main objective of this project is to increase the bio-availability of the Atorvastatin Calcium by delivering the drug at colon and as colon specific drug delivery system.

Materials and Methods

Materials:

Atorvastatin Calcium, β-cyclo dextrin (roquette),HPMC(Loba chem..Pvt.Ltd),HPC(Aqualon-hercules),Eudragit S100(Rohm gmbh pharma polymers),Eudragit L 100 (RGB polymers) PEG 6000 (Sd fine chem. .ltd).

Methodology: Plan of work



Atorvastatin Calcium is complexed with β-cyclo dextrin in (1:1) ratio by Co-evapouration method. Atorvastatin Calcium and β-cyclo dextrin were accurately weighed and dissolved in ethanol and water based upon solubility respectively.Both the solutions were mixed and solvents were evaporated by controlled heating 45°C-50°C.The dried mass were pulverized and sieved through sieve no.60.

Preparation of core tablet:

Atorvastatin Calcium tablet (120mg) was tried to compress with different directly compressible diluents like avicel 101,calcium carbonate and cross povidone was used as a super disintegrant ,HPMC,HPC,PVP are used as binders in this formulation with different concentrations. This mixture is blende and passed through 20#sieve and fines are separated using 40# sieve to obtain 20-40# mixture. Then lubricated with 2% talc and 1% magnesium stearate .The blend is compressed into tablets by using rotary tablet machine using 6mm round punch.This process is formulated for different binders and its concentration.The compositions of different formulations F1,F2,F3,F4,F5 and F6 were shown in the table

Table 3: Different formulations of atorvastatin calcium

S.no	Ingradient	CA1a		CA2		CA3	
		F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Atorvastatin calcium	21.7	21.7	21.7	21.7	21.7	21.7
2	β-cyclo dextrin	20	20	20	20	20	20
3	Micro crystalline cellulose pH-102	23.7	23.7	23.7	23.7	23.7	23.7
4	Calciumcarbonate	47.4	46.4	48.4	47.4	47.4	46.4
5	Crosspovidone	2	2	2	2	2	2
6	Sodium lauryl sulphate	0.1	0.1	0.1	0.1	0.1	0.1
7	Magnesium stearate	1	1	1	1	1	1
8	Colloidal Silicon dioxide	0.1	0.1	0.1	0.1	0.1	0.1
9	Talc	1	1	1	1	1	1
10	Hydroxyl propyl cellulose	3	4	-	-	-	-
11	Poly vinyl pyrollidineK30	-	-	2	3	-	-
12	Hydroxy propyl methyl cellulose	-	-	-	-	3	4
13	Total weight of tablet (mg)	120	120	120	120	120	120

Preparation of enteric coated and colon targeted tablets of Atorvastatin calcium:

The coating solution is prepared by PH sensitive olymers of Eudragit S100 and Eudragit L 100.These two polymers are optimized by changing the concentrations and combination ratios. Eudragit L100:Eudragit S100 in 1:1,1:4 and also with only Eudragit S100.

Table 4: Preparation of 5% coating solution

S.no	Ingradients	Weights (gm)		
		Only S100	4:1	1:1
1	**Eudragit S100**	5	4	1
2	**Eudragit L 100**	-	1	1
3	**Talc**	0.3	0.3	0.3
4	**PEG 6000**	4	4	4
5	**Acetone**	5ml	5ml	5ml
6	**Isopropyl alcohol**	90ml	90ml	90ml
7	**Water**	5ml	5ml	5ml

The coating dispersion was passed through sieve 0.25 mm aperture diameter before use.The spray rate and the bed temperature during the coating process were 2 gm/min (till the end of process) and 30-35°c respectively.before coating th e tablets were preheated to the 40°C bed temperature for 15 min.The tablets were coated to a 5,10,15 and 20%w/w total weight gain.

Table 5: Coating parameters Eudragit S100 and Eudragit L 100:S100(1:4) coating

Parameters	Specifications	
	Eudragit S100	Eudragit L 100:S100(1:4)
Batch size	50gm	50gm
Spray rate	2 gm/min	2 gm/min
Nozzle diameter	1 mm	1 mm
Atomizing air pressure	0.5 bar	1 bar
Air inlet temperature	50-60°C	30-35°C
Pan speed	30-40 RPM	50-60 RPM
Pre heating of core tablet	10 min	10min

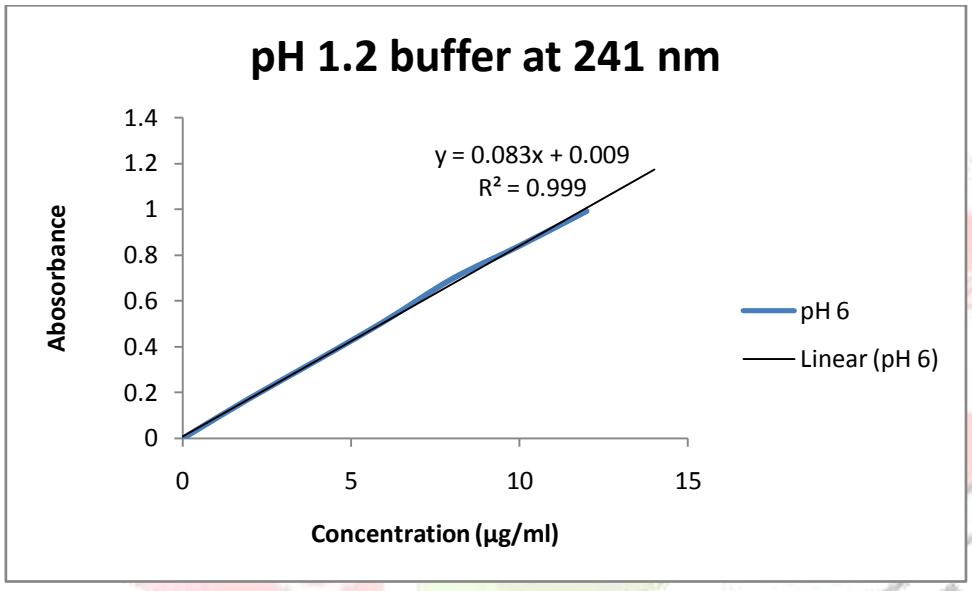
Results and Discussion

Standard Curve for Atorvastatin Calcium:

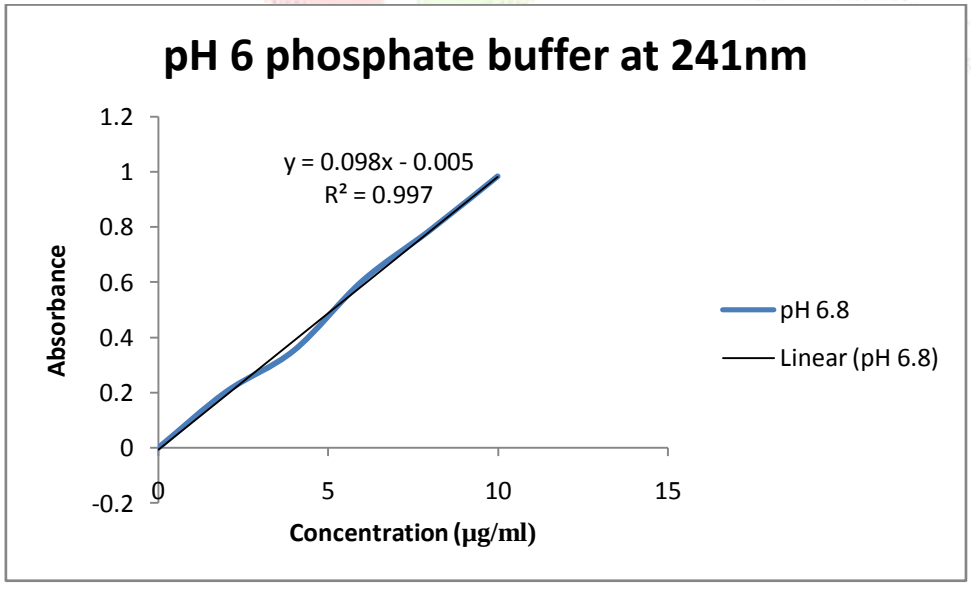
Table 6: Absorbance Values of Atorvastatin Calcium at different pH levels

S.No	Concentrations (µg/ml)	Absorbance At 241nm			
		pH 1.2	pH 6	pH 6.8	pH 7.2
1	0	0	0	0	0
2	2	0.148	0.176	0.203	0.202
3	4	0.289	0.342	0.353	0.319
4	6	0.426	0.512	0.603	0.476
5	8	0.558	0.696	0.787	0.629
6	10	0.704	0.84	0.983	0.781
7	12	0.816	0.992	-	0.923
8	14	0.944	-	-	-

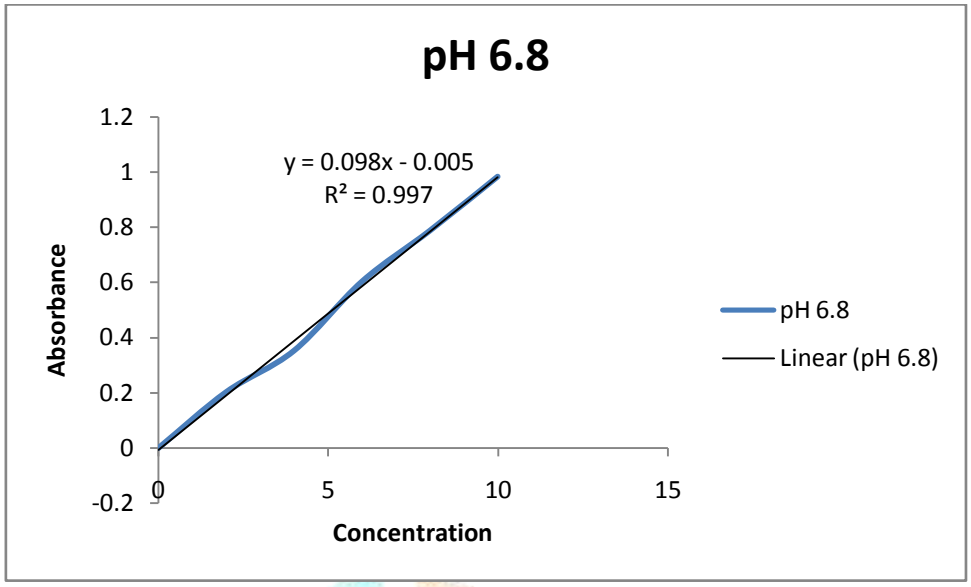
Standard graph of Atorvastatin Calcium in pH 1.2 buffer



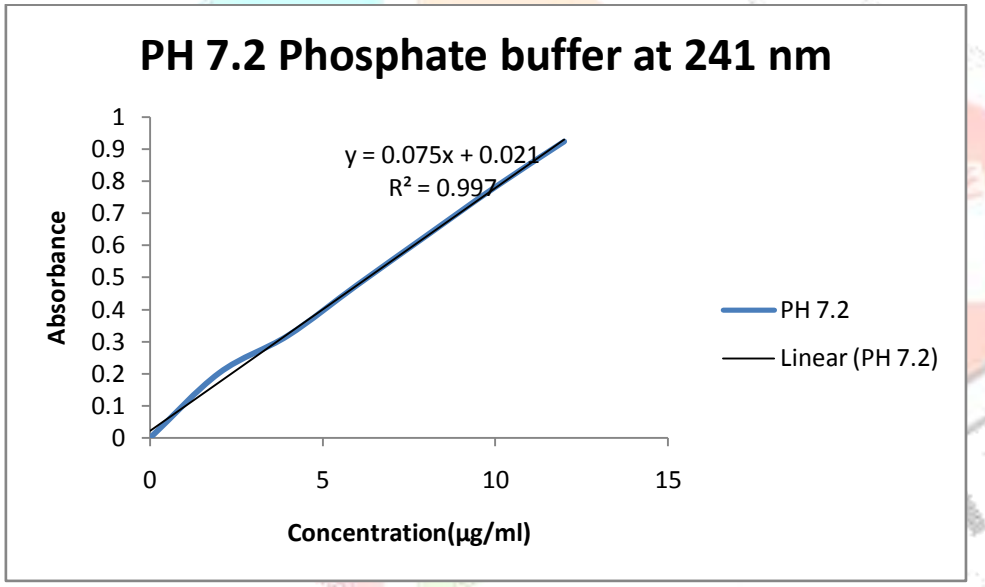
Standard graph of Atorvastatin Calcium in pH 6 phosphate buffer



Standard graph of Atorvastatin Calcium in pH 6.8 phosphate buffer



Standard graph of Atorvastatin Calcium in pH 7.2 phosphate buffer



Pre compression parameters:

Table 7: Bulk density , Tapped density, Angle of Repose, Average Particle size, Hausner Ratio of different formulations

S.no	Parameters	Drug	F1	F2	F3	F4	F5	F6
1	Bulk density (g/cm 3)	0.27	0.31	0.25	0.29	0.28	0.32	0.28
2	Tapped density (g/cm 3)	0.38	0.43	0.41	0.42	0.37	0.37	0.38
3	Angle of Repose	26.9°	27.2°	29.2°	27.6°	28.8°	26.5°	27.5°
4	Average Particle size (µm)	456.62	462.0	475.9	443.0	499.7	430.0	421.4
5	Hausner Ratio	1.40	1.38	1.64	1.44	1.32	1.16	1.35

Table 8: Post Compression Parameters:

Thickness, Hardness, Friability and Disintegration time of all formulations.

S.no	Formulation	Thickness (mm)	Hardness (N)	Disintegration time (min)	Friability (%w/w)
1	F1	6.13 – 6.26	238	4.8	0.192
2	F2	6.13 – 6.26	241	5.1	0.192
3	F3	6.11 - 6.23	240	4.9	0.195
4	F4	6.12 - 6.26	240	4.8	0.197
5	F5	6.10 - 6.23	239	5.1	0.196
6	F6	6.13 - 6.24	239	5.0	0.191

Table 9: Average Weight of All Formulations

Formulation	Weights
F1	1199-1201
F2	1199-1205
F3	1197-1201
F4	1198-1202
F5	1199-1201
F6	1198-1202

***Invitro* Release Studies:**

Table 10: *Invitro* percentage drug release of Atorvastatin calcium tablets with three different binders

S.no	Time	%Drug release		
		A1	A2	A3
1	0	0	0	0
2	5	12.9443	9.9383	10.4848
3	15	19.7763	18.9565	21.2338
4	30	27.8836	25.7885	23.0557
5	45	28.7945	31.8006	30.6164
6	60	27.8836	31.8917	28.1569
7	75	27.6103	30.6164	28.7034
8	90	27.5192	30.8897	29.3411

Table 11: *Invitro* percentage drug release of inclusion complex of Atorvastatin Calcium

S.no	Time	%Drug release				
		CA1a	CA1b	CA1c	CA2	CA3
1	0	0	0	0	0	0
2	5	21.6893	24.8775	19.9585	13.9464	16.8613
3	15	44.0071	35.4443	29.4322	29.7966	32.3472
4	30	58.1265	41.4565	38.2682	46.7399	44.9180
5	45	72.8836	54.3917	53.2986	68.3289	71.5172
6	60	76.4362	54.2095	47.0040	81.3553	76.9828
7	75	77.8937	56.9423	45.8289	80.1711	79.5334
8	90	75.4342	54.2095	46.0111	78.1670	72.8836

Table 12: *Invitro* % Drug Release of Atorvastatin Calcium with different concentrations of A1,A2 and A3 formulations

S.no	Time	%Drug release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	5	25.6974	31.9828	46.4666	35.8087	39.9079	31.4362
3	15	53.9362	55.5759	50.9302	49.2905	60.5860	47.5597
4	30	67.5091	63.5921	61.9524	55.7581	72.8836	65.1407
5	45	71.8816	66.3249	72.4281	60.6771	74.7966	67.6002
6	60	73.0820	72.6103	75.1609	62.4990	83.8897	72.2460
7	75	76.6184	75.2520	79.4423	60.2217	75.4342	68.8755
8	90	76.0719	76.8006	85.1832	57.3978	75.4342	67.8735

Table 13: *Invitro* % Drug Release of Atorvastatin Calcium tablets Formulation – F3 with coating of Eudragit S100

S.no	PH	Time	% Drug Release of F3(Coating with Eudragit S100)			
			20%	15%	10%	5%
1	0	0	0	0	0	0
2	1.2	60	0.5557	0.4646	3.0152	4.8370
3		120	0.7379	0.7379	3.6528	4.7460
4	6	180	0.5557	1.1933	7.5698	8.7540
5	6.8	210	0.1913	0.1913	8.4808	12.7621
6	7.2	240	0.1913	0.2824	9.6650	26.4261
7		270	0.1913	4.1043	13.4909	44.7358
8		300	4.4727	10.0294	17.7732	55.7581
9		330	4.7460	16.6791	19.5941	57.9443
10		360	4.8370	19.3209	18.6832	57.6711
11	6.8	365	4.5638	25.0597	28.5213	-
12		380	20.3229	29.0678	44.9180	-
13		410	34.1690	34.1690	46.1022	-
14		455	41.1832	41.1832	46.0111	-
15		470	45.5557	48.8350	45.9200	-
16		485	67.2358	61.7702	46.0111	-
17		500	77.8026	63.1366	46.1022	-

Table 14: *Invitro* % Drug Release of Atorvastatin Calcium tablets Formulation – F5 with coating of Eudragit S100

S.no	PH	Time	% Drug Release of F5(Coating with Eudragit S100)			
			20%	15%	10%	5%
1	0	0	0	0	0	0
2	1.2	60	0.4646	0.6468	2.3775	4.8370
3		120	0.8289	0.8289	2.6508	5.2014
4	6	180	0.5557	1.7399	5.9302	9.0273
5	6.8	210	0.2824	0.3735	9.0273	11.2136
6	7.2	240	0.2004	0.4281	13.4642	26.4261
7		270	0.1913	2.3047	17.5909	44.7358
8		300	4.8370	10.0294	19.3209	55.4848
9		330	3.1974	17.5901	22.4180	58.5820
10		360	5.0192	19.3209	21.4160	56.3957
11	6.8	365	5.5658	28.4302	30.8897	-
12		380	19.1387	35.5354	36.9929	-
13		410	35.0800	36.9929	41.0921	-
14		455	44.7358	50.5658	45.0091	-
15		470	46.9221	60.5860	43.2783	-
16		485	68.5111	61.7702	40.7277	-
17		500	79.7156	61.4970	43.2783	-

Table 15: *Invitro* % Drug Release of Atorvastatin Calcium tablets Formulation – F3 with coating of Eudragit L 100:Eudragit S100 (1:4)

S.no	PH	Time	% Drug Release of F5(Coating with Eudragit S100)			
			1:1		1:4	
			10%	20%	10%	20%
1	0	0	0	0	0	0
2	1.2	60	0.5557	0.2824	0.3735	0.5557
3		120	1.3755	1.1022	1.1933	0.9200
4	6	180	3.1974	2.4686	2.0132	1.1933
5	6.8	210	19.3209	16.7702	1.9221	0.7379
6	7.2	240	40.5455	25.0597	9.6650	0.4646
7		270	55.8492	55.4848	13.4909	2.5597
8		300	60.1306	56.3047	17.7723	14.1285
9		330	59.1285	63.2277	19.5941	14.8573
10		360	59.1296	68.6933	27.6103	20.8698
11	6.8	365	-	-	40.5455	22.1447
12		380	-	-	44.9180	31.7059
13		410	-	-	46.4666	35.5354
14		455	-	-	49.3816	49.1994
15		470	-	-	51.2945	54.2095
16		485	-	-	48.8350	60.3128
17		500	-	-	48.3796	53.1164

Table 16: *Invitro* % drug release of Atorvastatin Calcium tablet Formulation -F5 with Coating of Eudragit L 100:Eudragit S 100 (1:4)

S.no	pH	Time (min)	%Drug Release of F5(Coating with Eudragit L 100 :Eudragit S 100)	
			1:4	
			10%	20%
1	0	0	0	0
2	1.2	60	2.1953	0.5557
3		120	1.3755	0.9200
4	6	180	2.2864	1.1933
5	6.8	210	2.1043	0.7379
6	7.2	240	9.6650	0.4646
7		270	13.4909	2.5597
8		300	16.9524	14.1285
9		330	19.5941	19.2298
10		360	28.8856	26.0617
11	6.8	365	40.5455	34.8978
12		380	42.1852	40.9099
13		410	43.8249	44.1893
14		455	45.1002	46.4666
15		470	49.3816	53.8451
16		485	48.8350	55.5759
17		500	48.3796	54.7561

Table 17: Reports of Stability Study Formulations

S.no	Formulations	Storage Conditions	Testing Frequency	Reports
1	F3+Eudragit S100	Temp.25±2°C/ RH60±5%, Temp. 40±2°C/ RH 75±5%, Temp .60 ±2°C	Immediate submission after preparation at RT, 15 and 30 Days, 7 and 15 days	No change
2	F3 + Eudragit L 100 :Eudragit S100(1:4)			No change
3	F5+ Eudragit S100			No change
4	F5 + Eudragit L 100 :Eudragit S100(1:4)			No change

Conclusion

Atorvastatin a lipid lowering agent which has low solubility and low bio availability was prepared as a colon targeting coated tablet. Initially solubility of Atorvastatin was increased by complexing with β- cyclodextrin. β- cyclodextrin shows good release behavior with solubility improvement with ratio of drug : β-CD (1:1) ,the three optimized formulations were CA1a with 77.8%,CA2 with 81.35%,CA3 with 79.53% in 60 mins. These three formulations were prepared by using three different binders HPC (CA1a), PVP(CA2), HPMC(CA3). A total of 6 formulations (F1 to F6) were prepared by using different ratios of these three binders, a set of two with each binder then the coating was carried out for only F3&F5 formulas based upon the dissolution values of different binders concentration. These are coated with Eudragit S 100 and Eudragit L100:Eudragit S100 (1:4) with different coating levels. The good release shown in target area is F3 with 20% coating of Eudragit S100. The coating with Eudragit L100:Eudragit S100 (1:4) also gave similar release but the release time vary. it was observed that the drug release was controlled by increase in the coating level. Eudragit S 100 was used in different concentrations of 10% and 20% coating level. The F3 with 5%,10%,15%,20% coating showed a release of 55.75%,17.7%.9.8% and 4.43% respectively with in 5 hours, the coating levels of 5% and 10% release more than 10% wich is not acceptable. Howver the 15 % and 20% showed a release less than 10% in first 5 hours and 84.56% and 85.19% at the end of dissolution.The F5 formulaton with 15% and 20% coating also showed the similar results that Percentage of drug release was 10.01% and 4.99% in the first 5 hours and 83.9% and 84.66% at the end of the dissolution test. For these selected formulations the stability studies were conducted for one month with different storage conditions and testing frequency . The study results shows there was no change from initial tablets in physical and chemical properties of tablets.

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