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Formulation development and evaluation of colon targeted oral drug delivery system of atorvastatin

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ABSTRACT

The aim of the present work was to develop and evaluate colon specific sustained release tablet using Atorvastatin, coating material and matrix forming polymers. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different ratio of 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 incompatibility study by Fourier transform infrared spectroscopy (FTIR). Tablets were evaluated for micromeritic properties of granules, physical properties and drug content. 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 studies confirmed that, the designed formulation could be used potentially for colon delivery by controlling drug release in stomach and in intestine.

Keywords: Atorvastatin, Colon targeted drug delivery system, *in vitro* dissolution.

1. INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and gets absorbed from these regions of the gastrointestinal tract (GIT) depending upon the physicochemical properties of the drug[1]. The rectal route has traditionally been used to administer medicaments in the form of suppositories and enemas to the distal gut, although such formulations rarely succeed in spreading beyond the descending colon. However, colonic drug delivery via the oral route is not without its challenges. The colon constitutes the most distal segment of the gastrointestinal tract and so an orally administered formulation must retard drug release in the upper gastrointestinal regions but release the drug promptly on entry into the colon[2,3]. Numerous drug entities based on oral delivery have been successfully commercialized, but many others are not readily available by oral administration, which are incompatible with the physical and/or chemical environments of the upper gastrointestinal tract (GIT) and/or demonstrate poor uptake in the upper GIT [4]. Due to the lack of digestive enzymes, colon considered as suitable site for the absorption of various drugs.

During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents [5,6] . There are various methods or techniques through 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 systems [7,8]. Coating of the drugs with pH sensitive polymers provides simple approach for colon. Atorvastain 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 (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 objective of the present study was to develop a controlled release colon targeted drug delivery system of Atorvastain for the treatment of anti lipidemic agents.

2. MATERIALS AND METHOD

2.1. Materials

Atorvastain was provided as a gift sample by Hikal Ltd, (Hyderabad, India). Eudrajit L 100 D 55, Eudrajit S 100 and Shellac were from Loba chemicals, Mumbai. Other materials used in the study such as Calcium carbonate, Lactose mono hydrate, micro crystalline cellulose(Avicel PH 101), talc and Magnesium sterate were of pharmacopoeial grade. All the other chemicals were of analytical grade.

2.2. Methods

2.2.1. Formulation of Atorvastatin tablet

Atorvastatin Tablets was prepared by the wet granulation technique using water as granulating fluid, using the excipients like Calcium carbonate, Lactose mono hydrate, micro crystalline cellulose, talc and Magnesium stearate. The manufacturing process includes sifting, dry mixing, granulation (granulation was performed using lab model rapid mixer granulator – Make: Anchormark). The obtained wet mass was pass through sieve number 16 (mesh size: 1180 µm) and the sifted wet mass was dried in Fluid bed drier at 50°C for 2 hours- Make: Retsch).The dried granules are sifted through sieve no. 25 (mesh size: 710 µm) Final lubrication using Talc and Magnesium stearate in definite proportion was done using octagonal blender- Make: Anchormark. The blend was compressed into tablets with a target weight of 175mg, using 7 mm standard concave punches in 9 station, mini rotary, multi tooling compression machine (General Machinery Corporation)

The optimized formulation of tablet was coated using a combination of Eudragit L 100 and S100 by using a Pharma R&D coater (Ideal Cures) . 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 level (Cheng *et al.,* 2004).[9]

2.2.2. Preformulation studies

2.2.2.1. Fourier transforms Infrared spectroscopy

FT-IR spectra of Atorvastatin and physical mixture of Atorvastatin were recorded at room

Table - 1: Composition of Tablet formulations

Ingredients(mgs)	ACD-1	ACD-2	ACD-3	ACD-4	ACD-5
Atorvastatin calcium*	11.266	11.266	11.266	11.266	11.266
Calcium carbonate	35.000	35.000	35.000	35.000	35.000
Ethyl cellulose	10.000	20.000	30.000	40.000	50.000
Microcrystalline cellulose	35.734	30.754	30.734	25.734	35.734
Lactose Mono hydrate	73.000	68.000	58.000	53.000	33.000
Croscarmellose sodium	5.000	5.000	5.000	5.000	5.000
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	3.000	3.000	3.000	3.000	3.000
Magnesium Stearate	2.000	2.000	2.000	2.000	2.000
Core Tablet weight	175.000	175.000	175.000	175.000	175.000

*Quantity calculated based on conversion factor, LOD and Assay potency.

temperature condition using KBr pellet as carrier. KBr pellets were prepared by applying a pressure of 5-7 tons. IR spectrum was recorded using Shimadzu IR Prestige 21, measured at the maximum at 4000 cm^{-1} .

2.3. Evaluation of granules

2.3.1. Determination of bulk density and tapped density

An accurately weighed quantity of the granules (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus(electrolab). The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the formulae (Ashutosh *et al.,* 2008)[10]

Bulk density = W/V0 (g/ml)

Tapped density = W/Vf (g/ml)

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index % = (V0 - Vf) / V0 × 100

Hausner's ratio

Hausner's ratio was measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density/ Bulk density

Angle of repose

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of funnel just touches the heap of the blends. Accurately weighed blends are allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan\theta = h / r$$

Where, θ = Angle of repose, h = height of the pile, r = radius of plane surface occupy by the powder.

2.4. Evaluation of tablets

2.4.1. Tablet thickness

Thickness was measured using a calibrated Digital Vernier Caliber (Mitutyo). Three tablets of each formulation were picked randomly and thickness was measured individually.

2.4.2. Hardness

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

2.4.3. Friability

Friability of tablets was determined using Tablet Friability Tester (Electrolab). 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 revolution (Hausner *et al.,* 1967) [11]. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula,

F = Wi - Wf / Wi × 100

2.4.4. 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 variation [12] (Carr and Hausner *et al.,* 1995).

2.4.5. Drug Content

The drug content (assay) of the selected formulation ACD-5 was tested as per analytical method from IP.

2.4.5.1. *In –vitro* dissolution studies

The release rate of atorvastatin colon specfic tablets were determined using USP dissolution testing apparatus II Paddle. The test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5°C and 75 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.[13]

3. RESULTS AND DISCUSSION

3.1. IR studies

Drug polymer interaction when studied by FT-IR, showed no drug: excipient interaction. From the FTIR spectrum above interpretation it is understood that there is no major shifting in the frequencies of above said functional groups of

atorvastatin was identified which indicates that there is no chemical interaction between atorvastatin and polymer which were used in the formulations. It is given in figure 1 and 2.

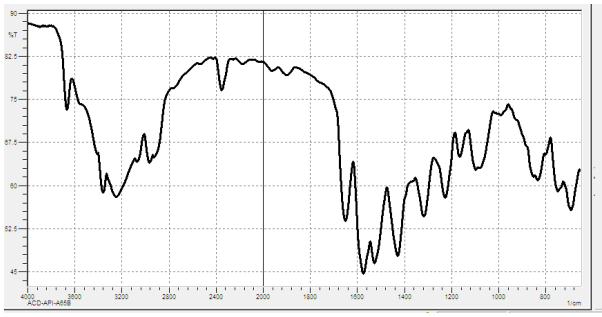

Figure - 1: FT-IR spectrum of Atorvastatin

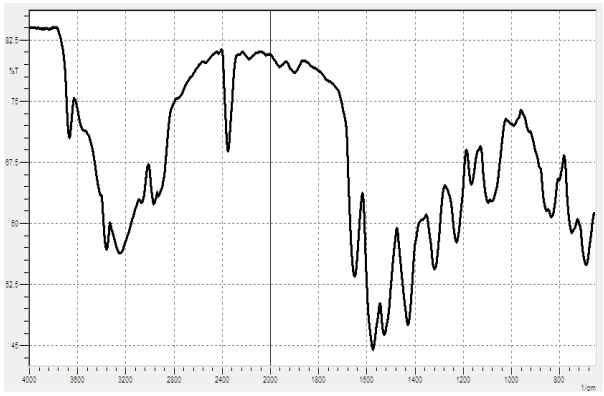

Figure - 2: FT-IR spectrum of Atorvastatin + physical mixture.

3.2. Micromeritic properties

The micromeritic properties of all the formulations were compared and it was found that ACD-5 was optimal and within specified limits. The micromeritic properties of various formulations are given in table 2. Different formulations of tablets were formulated using wet granulation for which the granules were subjected to various micromeritic parameters. Angle of repose ranged from 19.09° to 24.93° and the Carr's compressibility index ranged from 14.428 to 17.63. The bulk density and tapped bulk density of the prepared blend ranged from 0.446 to 0.562g/ml and 0.525 to 0.735 g/ml respectively. The results of angle of repose indicates good flow property of the powder and the value of Carr's compressibility index further showed support for the flow property (Table 2). All the formulation possessed good flow properties. Low value of angle of repose, Carr's index and Hausner's ratio (Table 2) revealed good micromeritic behaviour of the granules. Since, the flow properties of the powder mixture are important for the uniformity of dose of the tablets; ACD5 was found to be the best among all the tablet formulations due to low Hausner's ratio, Carr's index and angle of repose.

3.3. Physical properties

The physical properties of colon targeted tablet of atorvastatin was presented in the table 3.Tablets were also evaluated for the hardness using digital hardness tester (Schleuniger), friability using a Tablet friability Tester (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/cm^2, 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 to100.24± 0.67 % which is within acceptable limits.

3.4. In vitro drug release studies

The compression coated tablets containing 10mg of atorvastatin were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of atorvastatin from compression coated tablets was carried out using USP dissolution apparatus type II paddle at a rotation of 75 RPM and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 4 hours, as the average small intestinal transit time is about 4 hours, and finally simulated colonic fluid (SIF, pH 6.8) was used upto 24 hours to mimic colonic pH conditions. Drug release was measured from compression coated atorvastatin tablets, added to 900 ml of dissolution. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed HPLC methods. All dissolution studies were performed for 5 formulation trials.

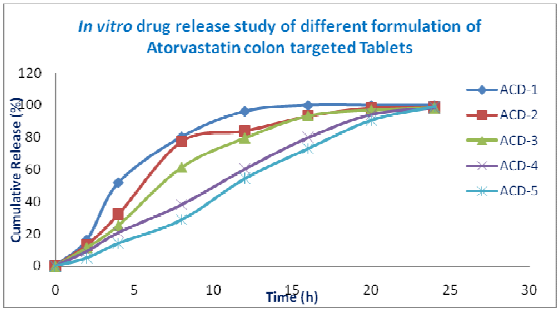

Figure - 3: *In vitro* drug release study.

Table - 2: Evaluation of preformulation paramaters Micromeritic of Atorvastatin colon target tablets

Formula	Angle of repose (0)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	*Hausner's ratio*
ACD-1	24.93 ± 1.21	0.562 ± 0.023	0.735 ± 0.036	17.63 ± 0.52	1.30 ± 0.021
ACD-2	23.87 ± 1.62	0.540 ± 0.042	0.655 ± 0.034	16.42 ± 0.44	1.21 ± 0.023
ACD-3	22.81 ± 1.51	0.543 ± 0.046	0.645 ± 0.043	15.98 ± 0.34	1.81 ± 0.032
ACD-4	20.78 ± 1.52	0.486 ± 0.024	0.595 ± 0.034	15.42 ± 0.42	1.22 ± 0.022
ACD-5	19.07 ± 1.34	0.446 ± 0.034	0.525 ± 0.022	14.42 ± 0.64	1.17 ± 0.032

All values are expressed mean of 3 determination ± standard deviation

Table - 3: Physicochemical parameters of developed colon targeted tablets of Atorvastatin

Parameters	ACD-1	ACD-2	ACD-3	ACD-4	ACD-5
Hardness (Kg/cm2)	5.4± 0.35	5.2± 0.42	5.2± 0.32	5.0± 0.42	4.6± 0.28
Friability (%)	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
Wt. variation Before coating (mgs)	175.82± 0.22	175.42± 0.27	175.44± 0.43	175.34± 0.34	175.22± 0.45
Wt. Variation After coating (mgs)	190.42± 0.34	191.56± 0.32	191.76± 0.45	190.87± 0.46	191.22± 0.22
Drug content (%)	99.13± 0.67	99.66± 0.88	99.71± 0.92	99.72± 0.22	100.24± 0.26

All values are expressed mean of 3 determination ± standard deviation

Table - 4: *In vitro* drug release study of different formulation of Atorvastatin colon targeted Tablets

Dissolution Media	pH	Time (Hrs)	Formulations				
			ACD-1	ACD-2	ACD-3	ACD-4	ACD-5
Simulated gastric fluid	1.2	2	16.23	13.12	11.42	9.12	5.00
Simulated Intestinal fluid	7.4	4	51.88	32.12	25.25	20.76	14.12
Simulated colonic fluid	6.8	8	80.22	77.34	61.41	38.18	28.76
Simulated colonic fluid	6.8	12	96.14	83.89	79.60	60.34	54.34
Simulated colonic fluid	6.8	16	99.76	93.12	93.44	79.87	72.98
Simulated colonic fluid	6.8	20	-	98.24	97.08	94.33	90.65
Simulated colonic fluid	6.8	24	-	98.66	98.37	98.37	99.13

The release of atorvastatin from colon targeted tablets varied according to the types and proportion of polymers content in the various formulations. The progressive decrease in the amount of drug release from formulations ACD4 and ACD5 attributed to gradual increase the amount of Ethyl cellulose contents. Formulations ACD 1 to ACD 5 contains ethyl cellulose different concentration. 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.

4. 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. Atorvastatin colon targeted different formulations were developed by using release rate controlling

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 . Developed film coated colon targeted tablets possessed the required physicochemical parameters such as hardness, friability, weight variation, drug content. Drug release studies shows that ACD5 shows good release behaviour in colon and restricts release in stomach and intestine as compare to ACD1 to ACD5. From the above investigation it was observed that formulation ACD5 was found to be best among the prepared formulations which may be used for prolong drug release in colon for, thereby improving patient compliance and bioavailability.

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