



FORMULATION DEVELOPMENT AND EVALUATION OF COLON TARGETED ORAL DRUG DELIVERY SYSTEM OF AZILSARTAN MEDOXAMIL

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ABSTRACT

The aim of the present work was to develop and evaluate colon specific sustained release tablet using Azilsartan Medoxamil, coating material and matrix forming polymers. Colon targeted tablets were prepared in two steps. Initially core tablets Azilsartan Medoxamil were prepared by wet granulation method using different concentration of, microcrystalline cellulose as filler, mannitol as diluents, croscarmellose sodium as disintegrating agents, hydroxyl propyl cellulose as sustained release polymer, magnesium stearate was used as a glidant and lubricant respectively. 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 incompatibility study by Fourier transform infrared spectroscopy (FTIR). The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. All the batches of matrix tablet (AM1-AM5) were subjected for *in-vitro* dissolution in various simulated gastric fluids for suitability for colon specific drug delivery system. The amount of Azilsartan Medoxamil released from tablets at different time intervals was estimated by RP-HPLC methods. Among all the formulations AM5 formulation was found to be optimized as it was retarded the drug release up to 24 hours and showed maximum of 99.79 cumulative percentage drug release. The studies confirmed that, the designed formulation could be used potentially for colon delivery by controlling drug release in stomach and the small intestine.

KEYWORDS: Azilsartan Medoxamil, wet granulation, hydroxyl propyl cellulose, Eudragit L100 and S100.

INTRODUCTION

Azilsartan medoxamil is (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-([2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-1H-benzimidazole-7-carboxylate. It is an angiotensin-II receptor antagonist has been widely used for the treatment of hypertension. The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration.^[1,2] Due to the lack of digestive enzymes, colon is considered as suitable site for the absorption of various drugs. Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes and temporary storage

of stools. But now it is accepted as important site for drug delivery.^[3,4] Majority of the research has focused on delivery of drug to the small intestine. The large intestine, however, because of its remoteness and relatively different physiology acquired the status of an outcast. From last two decades, interest in area development of oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders.^[5]

An ideal drug delivery system specifically to the colon avoids the drug release in stomach and small intestine, but begins delivery at the beginning of the large bowel where conditions are most favourable for drug dispersion and absorption. To achieve successful colon targeting, it should overcome the following limitations.^[6,7] Treatment might be more effective if the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and, if so, systemic side

effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted on the colon. Site-specific means of drug delivery could also allow oral administration of peptide and protein drugs, which normally become inactivated in the upper parts of the gastrointestinal tract.^[8,9]

CTDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis.^[10] Colonic drug delivery can be achieved by oral or rectal administration. With regard to rectal route, the drugs do not always reach the specific sites of the colonic disease and the sites of colonic absorption. To reach the colon and to be able to specifically deliver and absorb the drug there, the dosage form must be formulated taking into account the obstacles of gastrointestinal tract. The objective of the present investigation was to develop a controlled release colon targeted drug delivery system of Azilsartan Medoxamil.

MATERIALS AND METHOD

Materials

Azilsartan Medoxamil was provided as a gift sample by Hydrodrugs Ltd, Hyderabad, India. Eudrajit L 100 D 55, Eudrajit S 100 were purchased from Loba chemicals, Mumbai. Other materials used in the study such as mannitol, micro crystalline cellulose (Avicel PH 101), Croscarmellose sodium, hydroxyl propyl cellulose,

povidone and Magnesium stearate were of pharmacopoeial grade. All the other chemicals were of analytical grade.

Methods

Formulation of Azilsartan Medoxamil tablet

Azilsartan Medoxamil 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 AM are shown in Table 1. The powders (AM1-AM5) 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 magnesium stearate in definite proportion. The lubricated granules were compressed in to the tablets with the target weight 150mg, using 7.1mm standard concave punches. Cadmach Mini Rotary Tablet Press (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 level.^[11]

Table 1: Composition of Tablet formulations

Ingredients(mgs)	AM-1	AM-2	AM-3	AM-4	AM-5
Azilsartan Medoxamil	21.380	21.380	21.380	21.380	21.380
Mannitol	68.000	64.500	60.000	57.500	54.000
Micro crystalline cellulose	44.620	49.620	54.620	59.620	64.620
Croscarmellose sodium	11.500	10.000	9.000	6.000	4.000
Povidone	3.000	3.000	3.000	3.000	3.000
Hydroxy propyl cellulose	1.000	1.000	1.500	1.750	1.500
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium stearate	0.500	0.500	0.500	0.750	1.500
Core Tablet weight	150.000	150.000	150.000	150.000	150.000

Preformulation studies

Fourier transforms Infrared spectroscopy

FT-IR spectra of Azilsartan Medoxamil and physical mixture of Azilsartan Medoxamil were recorded at room temperature condition using KBr pellet technique. KBr pellets were prepared by applying a pressure of 5-7 tons. IR spectrum was recorded using Perkin Elmer Spectrum GX FT-IR, measured at the maximum at 4000 cm⁻¹ using methanol as a blank.

Evaluation of granules

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. The density apparatus was set for 100 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the formulae^[12,13]

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

Compressibility index^[12,13]

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

$$\text{Carr's index \%} = (V_0 - V_f) / V_0 \times 100$$

Hausner's ratio^[12,13]

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

Hausner's ratio = Tapped density/ Bulk density

Angle of repose^[12,13]

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.

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 revolution.^[14] 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 variation.^[15]

Drug content

The matrix tablets were tested for their drug content following crushing and powdering five tablets from each batch separately. The amount of powder equivalent to 500 mg of the drug was weighed and dissolved in 100mL of distilled water. After 10 minutes of centrifugation, aliquots of 1mL were taken from this solution and diluted to 100mL with water (10 μ g/mL). The drug

content was estimated by using RP HPLC method. The chromatographic conditions like column was used zorbax SB C 18 150 \times 4.6mm, 3.5 μ or equivalent flow rate was fixed 0.8ml/min, injection volume 10 μ l and of run time 30min and absorbance wavelength was 220nm was measured in a RP HPLC . Drug content was calculated.

IN –VITRO DISSOLUTION STUDIES^[16]

The compression coated tablets containing 20mg of Azilsartan Medoxamil were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of Azilsartan Medoxamil from compression coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37 \pm 0.5 $^{\circ}$ 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 Azilsartan Medoxamil 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 RP HPLC methods. All dissolution runs were performed for 5 formulation trials.

Stability studies

Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, colour, odour, taste or texture of the formulation indicate the drug instability. Among the five enteric coated Formulation, Formulation AM5 was selected for stability studies based on the physicochemical characterization of coating films and release characteristics. The stability studies were carried out at 40 \pm 2 $^{\circ}$ C with 75 \pm 5% RH.

RESULTS AND DISCUSSION**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 Azilsartan Medoxamil was identified which indicates that there is no chemical interaction between Azilsartan Medoxamil and polymer which were used in the formulations. It is given in figure 1 to 7.

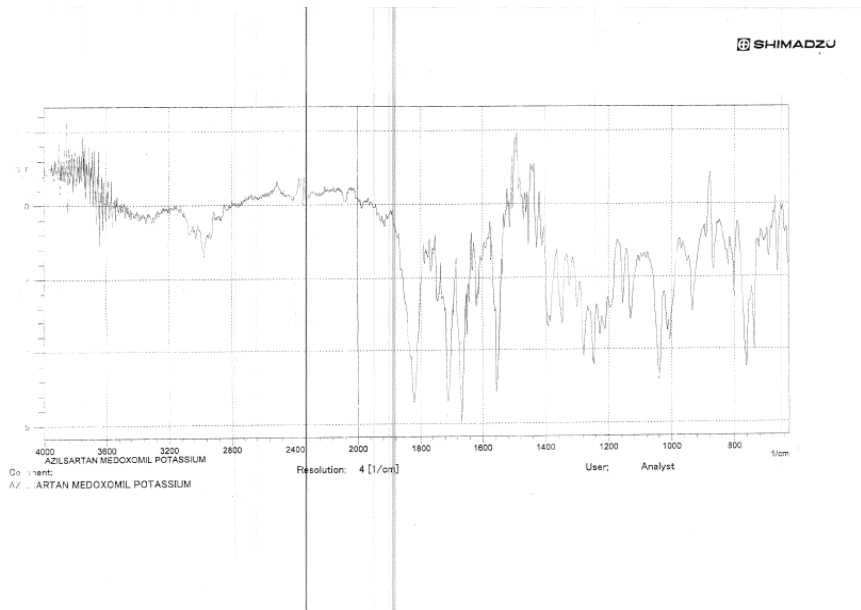


Fig. 1: FT-IR spectrum of Azilsartan Medoxamil

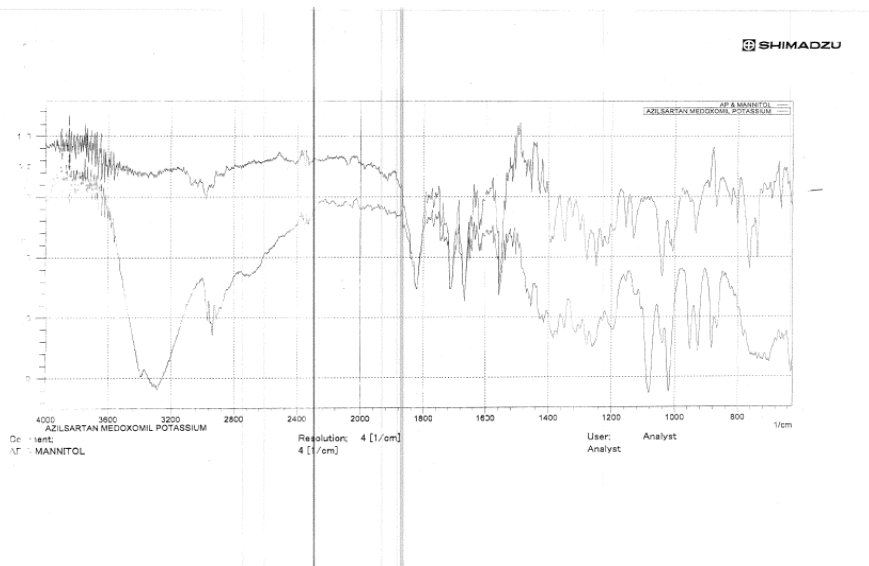


Fig. 2: FT-IR spectrum of Azilsartan Medoxamil+ Mannitol

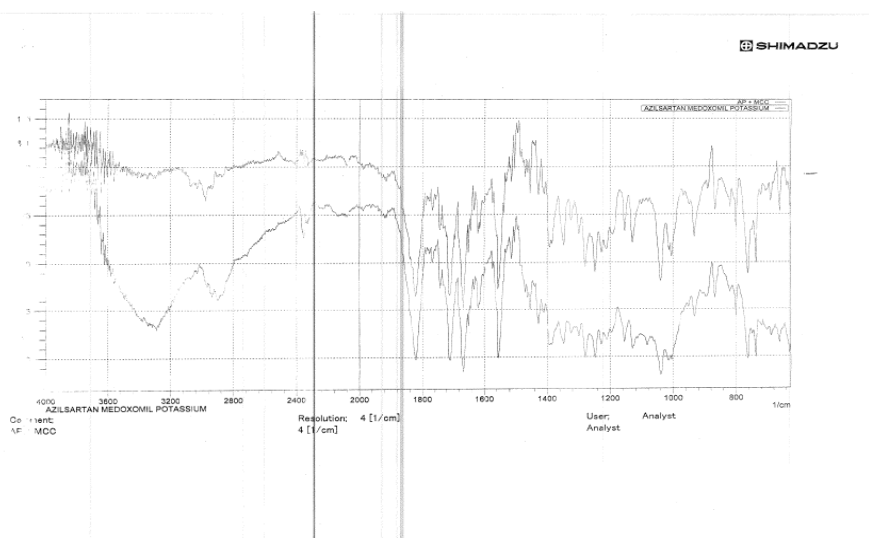


Fig.3: FT-IR spectrum of Azilsartan Medoxamil+ MCC

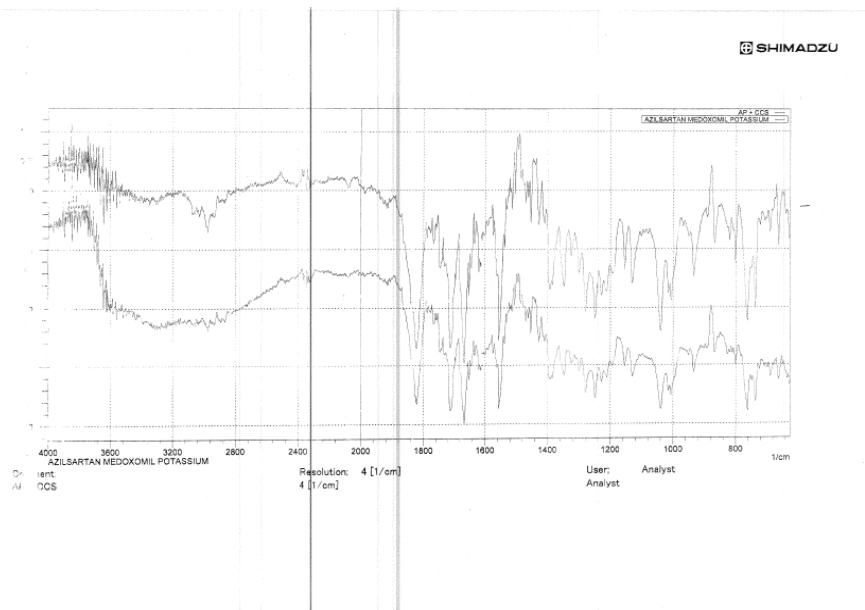


Fig.4: FT-IR spectrum of Azilsartan Medoxamil+ CCS

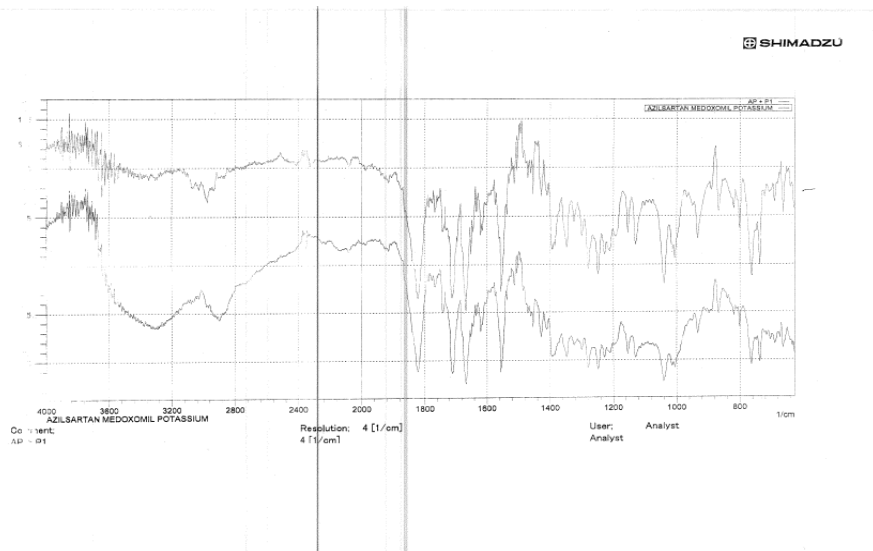


Fig.5: FT-IR spectrum of Azilsartan Medoxamil+ Povidone

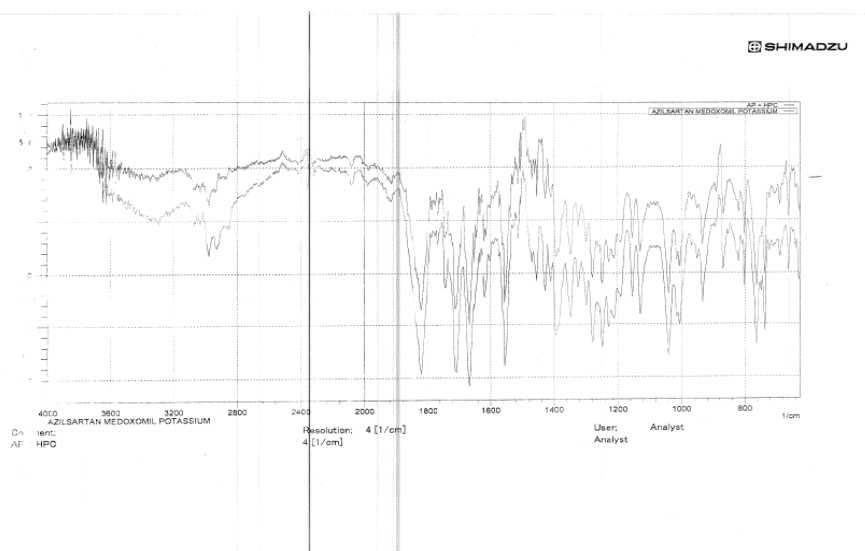


Fig.6: FT-IR spectrum of Azilsartan Medoxamil+ HPC

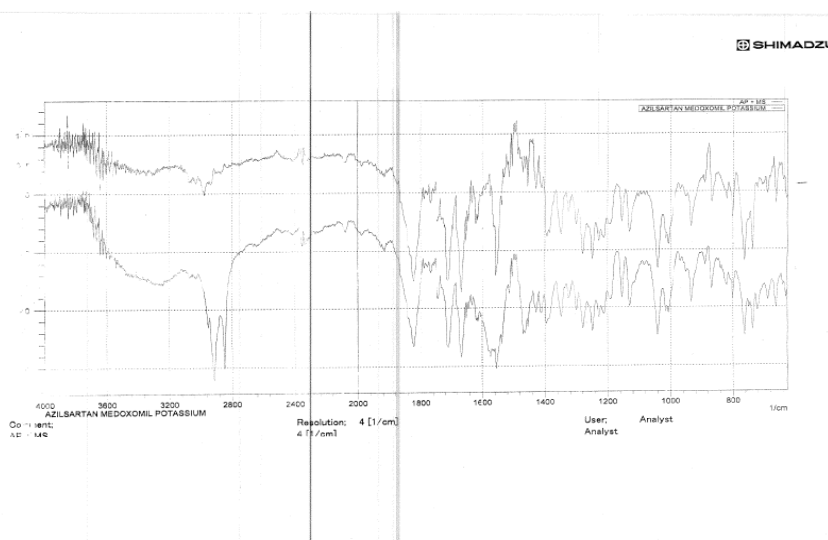


Fig.7: FT-IR spectrum of Azilsartan Medoxamil+ Magnesium stearate

Micromeritic properties

The micromeritic properties of all the formulations were compared and it was found that AM-5 was optimal and within specified limits. The micromeritic properties of various formulations are presented in table 2. Various formulations of tablets were formulated using wet granulation for which the granules were subjected to different micromeritic parameters. Angle of repose ranged from 20.32° to 25.78° and the Carr's compressibility index ranged from 13.32 to 17.75. The bulk density and tapped bulk density of the prepared blend ranged from 0.468 to 0.578g/ml and 0.565 to 0.689 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 behavior of the granules. Since, the flow properties of the powder mixture are important for the uniformity of dose of the tablets; AM5 was found to be the best among all the tablet

formulations due to low Hausner's ratio, Carr's index and angle of repose.

Physical properties

The physical properties of colon targeted tablet of Azilsartan Medoxamil was presented in the table 3. 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 6.90-7.00 mm. The hardness for various formulations was found to be between 3.2 to 3.9 kg/cm², indicating satisfactory mechanical strength. The friability of the uncoated tablets of various formulations were found in 0.38 ± 0.024 to 0.52 ± 0.043 and weight variation of uncoated tablets of different tablet formulations were found in compendial limits, i.e. 149.67 ± 0.54 to 153.34 ± 0.34 respectively, which is an indication of good mechanical resistance of the tablet. Drug content was found to be in the range of 98.67 ± 0.24 to $101.76 \pm 0.44\%$ which is within acceptable limits.

Table: 2 Evaluation of preformulation parameters Micromeritic of Azilsartan Medoxamil colon target tablets

Formula	Angle of repose (°)	Bulk density gm/ml	Tapped density gm/ml	Carr's index %	Hausner's ratio
AM-1	25.78 ± 1.25	0.578 ± 0.032	0.689 ± 0.046	16.11 ± 0.48	1.19 ± 0.012
AM-2	22.64 ± 1.42	0.566 ± 0.90	0.676 ± 0.024	16.27 ± 0.28	1.11 ± 0.026
AM-3	23.57 ± 1.23	0.468 ± 0.034	0.565 ± 0.056	17.16 ± 0.42	1.20 ± 0.036
AM-4	21.24 ± 1.22	0.556 ± 0.034	0.676 ± 0.024	17.75 ± 0.48	1.21 ± 0.034
AM-5	20.32 ± 1.65	0.553 ± 0.028	0.638 ± 0.022	13.32 ± 0.42	1.15 ± 0.042

All mean values are expressed of 3 determination \pm standard deviation

Table: 3 Physicochemical parameters of developed colon targeted tablets of Azilsartan Medoxamil

parameters	AM-1	AM-2	AM-3	AM-4	AM-5
Hardness Kg/cm ²	3.4 ± 0.65	3.2 ± 0.24	3.8 ± 0.72	3.6 ± 0.26	3.9 ± 0.45
Friability % loss	0.38 ± 0.024	0.52 ± 0.043	0.48 ± 0.024	0.50 ± 0.052	0.44 ± 0.043

Thickness mm	6.90±0.022	6.92±0.044	6.94±0.022	6.95±0.024	7.0±0.044
Weight Variation Before Coating mgs	152.22± 0.12	153.34± 0.34	152.48± 0.38	149.67± 0.54	151.22± 0.23
variation After coating mgs	175.24± 0.14	176.76± 0.34	174.42± 0.56	176.62± 0.36	176.22± 0.42
Drug content %	101.76± 0.44	99.26± 0.78	98.67± 0.24	98.92± 0.25	99.87± 0.42

All mean values are expressed of 3 determination ± standard deviation

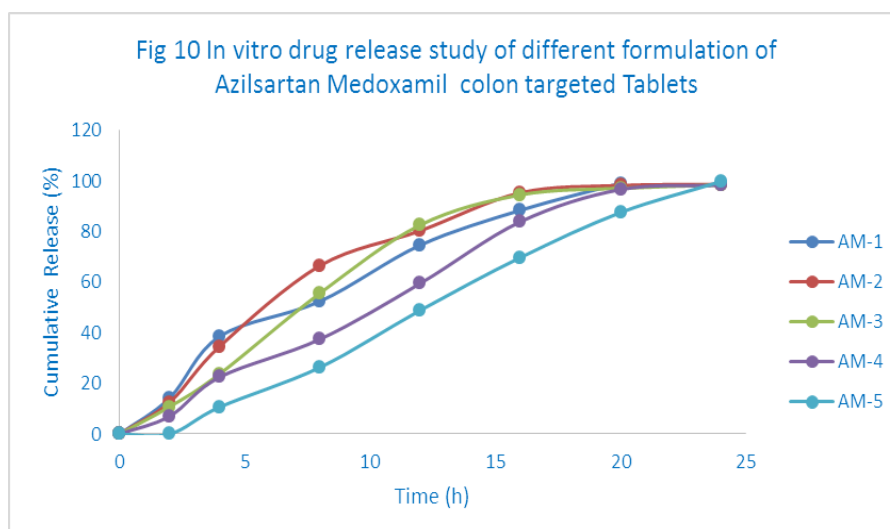
IN VITRO DRUG RELEASE STUDIES

The cumulative percentage releases of different formulation of Azilsartan Medoxamil colon targeted tablets were shown in Table 4 and Figure 8. The release of Azilsartan Medoxamil from colon targeted tablets varied according to the types and proportion of polymers content in the various formulations. Formulation which shows most satisfactory result is AM5, where drug release started after 2 hrs, and released maximum 99.79 by 24 hrs. Remaining formulations were respectively,

release started and reached maximum, AM1- 2hrs in 14.45 and 99.12 in 20 hrs, AM2-12.56 in 2 hrs and 98.66 in 24 hrs, AM3-10.78 in 2hrs and 98.45 in 24 hrs, AM4-7.04 in 2 hrs and 98.37 in 24 hrs. Formulations AM 1 to AM 5 contains hydroxyl propyl cellulose different concentration. As the concentration of hydroxyl propyl cellulose increases retardation nature also increased. The duration of drug release was slower with formulation AM5 which was about only 99.79 % in 24 hrs.

Table: 4 The *In vitro* cumulative percentage release study of different formulation of Azilsartan Medoxamil colon targeted Tablets

Dissolution Media	Time (Hrs)	Formulations(cumulative percentage drug release)				
		AM-1	AM-2	AM-3	AM-4	AM-5
Simulated gastric fluid	2	14.45	12.56	10.78	7.04	0.0
Simulated intestinal fluid	4	38.65	34.67	23.78	22.54	10.67
Simulated colonic fluid	8	52.44	66.54	55.65	37.46	26.34
Simulated colonic fluid	12	74.64	80.34	82.62	59.52	48.89
Simulated colonic fluid	16	88.45	95.34	94.54	83.90	69.76
Simulated colonic fluid	20	99.12	98.24	97.12	96.65	87.56
Simulated colonic fluid	24	-	98.66	98.45	98.37	99.79



Stability studies

Among the five Formulation, Formulation AM5 was selected for stability studies based on the physicochemical characterization of coating films and

release characteristics. The stability studies were carried out at 40 ± 2 °C with $75 \pm 5\%$ RH . There were no significant changes in their physical appearance, average weight of tablets and hardness. It was observed that the

initial drug content and the drug contents of the samples analyzed after 1,3 and 6 month of storage were similar. The release profile also not showed any significant changes indicating that there were no significant changes

in the physical as well as chemical characteristics of the formulation. Hence, it can be concluded from the results that the developed tablets were stable and retain their pharmaceutical properties over a period of 6 month.

Table.5.Stability studies of Azilsartan Medoxamil colon targeted Tablets formulation AM5

Evaluation parameters	Observation in month			
	Initial	1 st month	3 rd month	6 th month
Physical appearance	white colour tablets	white colour tablets	white colour tablets	white colour tablets
Hardness (Kg / cm ²) *	3.9 ± 0.24	3.9 ± 0.24	3.9 ± 0.28	3.9 ± 0.26
Drug Content (%)*	100.42 ± 0.12	99.94 ± 0.58	99.86 ± 0.24	99.66 ± 0.46

*All values are expressed mean of 3 determination ± standard deviation

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. Azilsartan Medoxamil colon targeted different formulations were developed by using release rate controlling polymers like hydroxy propyl cellulose by wet granulation methods and then the tablets were enteric coated with Eudragit polymers (L-100 and S-100; 1:1) polymers.

From the reproducible results obtained from the executed experiments it can be concluded that Eudragit polymers (L-100 and S-100; 1:1) polymers can be used as enteric coated polymer. Both the polymer can protect the drug from the acid environment that is in gastric pH and release the drug when it's reached in intestinal pH. Hence, formulation of Azilsartan Medoxamil as an enteric coated tablet may solve the stability problem of drug in the stomach and release the drug in the intestine. After satisfied pre-compression and post compression result the of core tablets, tablets were coated with suitable coating material to develop the dosage form which is to overcome the drug degradation by the gastric enzymes as well as the acidic environment of the stomach. From the above investigation it was observed that formulation AM5 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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