Research Article

Formulation Development and *In Vitro* Evaluation of Azilsartan Medoxomil Colon Targeted Drug Delivery System

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ABSTRACT

The objective of the present work was to design, develop and evaluate colon specific sustained release tablet using Azilsartan Medoxomil, coating material and matrix forming polymers. Colon targeted tablets were prepared in five formulations with different polymers by wet granulation method. Eudragit L100 and S100 were used as enteric coating polymers. Drug and physical mixture were evaluated for incompatibility study by DSC. 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. 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 release kinetics showed that increase the amount of polymers become the drug release rate more controlled manner. The release profiles of AM3, AM4 and AM5 might be well clarified by Higuchi model, as the plots showed good linearity and correlation coefficient (R2) values 0.883, 0.915 and 0.956 respectively. The studies confirmed that, the designed formulation could be used potentially for colon delivery by controlling drug release in colon.

Keywords: Azilsartan Medoxomil, wet granulation, Eudragit L100 and S100, release kinetics.

INTRODUCTION

Azilsartan medoxomil 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 anangiotensin-II receptor antagonist has been widely used for the treatment of hypertension. Ongoing research in the area of oral delivery of drugs, a discipline which has basked in the spotlight of pharmaceutical sciences for the past 70 years, has led to improved and profound insights into the physiology, biology and physical chemistry (pharmacokinetics, partitioning phenomenon) of organs, compartments, cells, membranes, cellular organelles and functional proteins (e.g. transporters) associated with absorption processes of drugs in the gastrointestinal tract (GIT). 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[1].

In recent years, colon targeted delivery systems have been the focus point of formulation laboratories because the colon[2] 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 infections[3], and constipation, which require local delivery of the drug. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters 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 very well[4,5].

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].

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 design and development and in vitro evaluation of colon targeted drug delivery system of Azilsartan Medoxamil.

MATERIALS AND METHOD

Materials

Azilsartan Medoxomil was provided as a gift sample by Hetero drugs 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 Medoxomil Tablets was prepared by the wet granulation technique using 2% povidone solution. 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 povidone solution. The obtained wet mass was passed through sieve number 16 (mesh size: 1000 µm) and the granules were dried at 50º 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 Machinary Co Pvt. Ltd

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[10]

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	53.000	48.500	45.000	37.500	30.000
Micro crystalline cellulose	35.620	34.620	41.120	41.370	42.120
Croscarmellose sodium	11.500	10.000	9.000	6.000	4.000
Povidone	3.000	3.000	3.000	3.000	3.000
HPMC K100M	25.000	32.000	30.000	40.000	48.000
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

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-60 instrument. The drug-excipient mixture was scanned in the temperature range of 50-400 ^{0}C under the atmosphere of nitrogen. Aluminium pans and lids were used for all samples. The heating rate was 20 ^{0}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 revolution[11]. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula,

$$F = Wi - Wf / Wi \times 100$$

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[12] .

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

***In –vitro* Dissolution Studies[13]**

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±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 up to 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.

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)[14] (Higuchi *et al.,* 1963), Hixson–Crowell model[15] and Korsmeyer-Peppas[16] (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 MS Excel 2007. The model with the highest correlation coefficient was considered to be the best fitting one[17] (Dorozynski *et al.,* 2004).

RESULTS AND DISCUSSION

Differential scanning calorimetry studies

Thermograms were obtained for pure Azilsartan Medoxamil and mixed matrix containing Azilsartan Medoxamil with other excipients. Pure powdered Azilsartan Medoxamil showed a melting endotherm at 212°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 Figure 1 to 3.

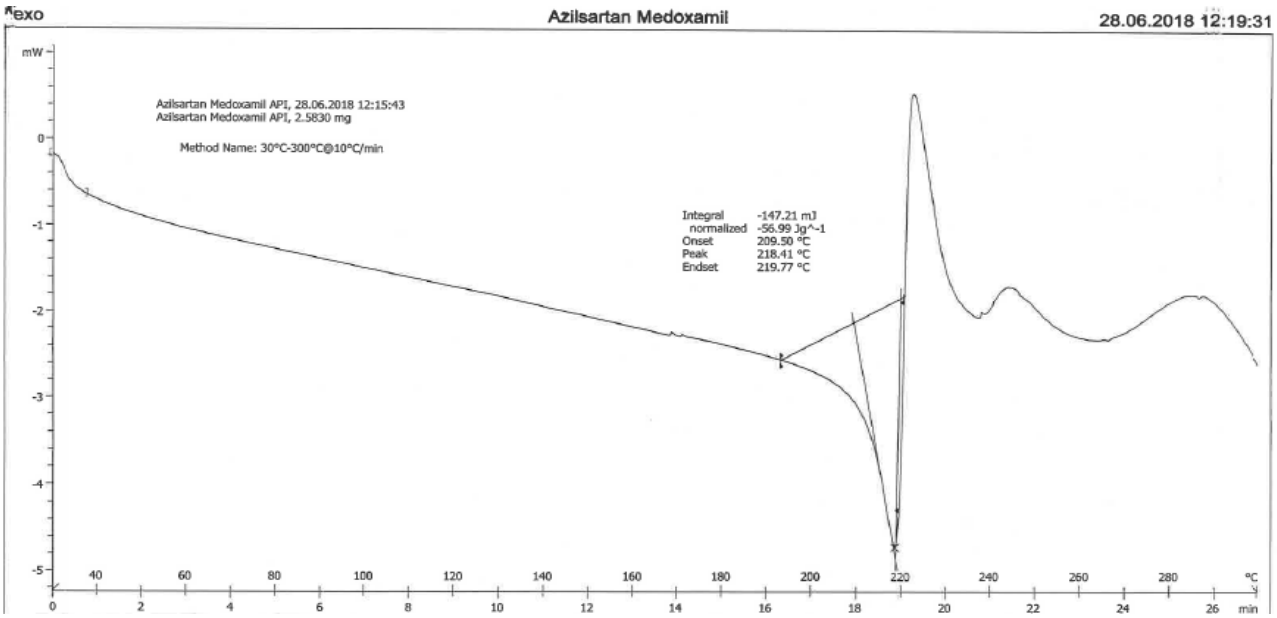


Figure 1: DSC spectrum of Azilsartan Medoxamil

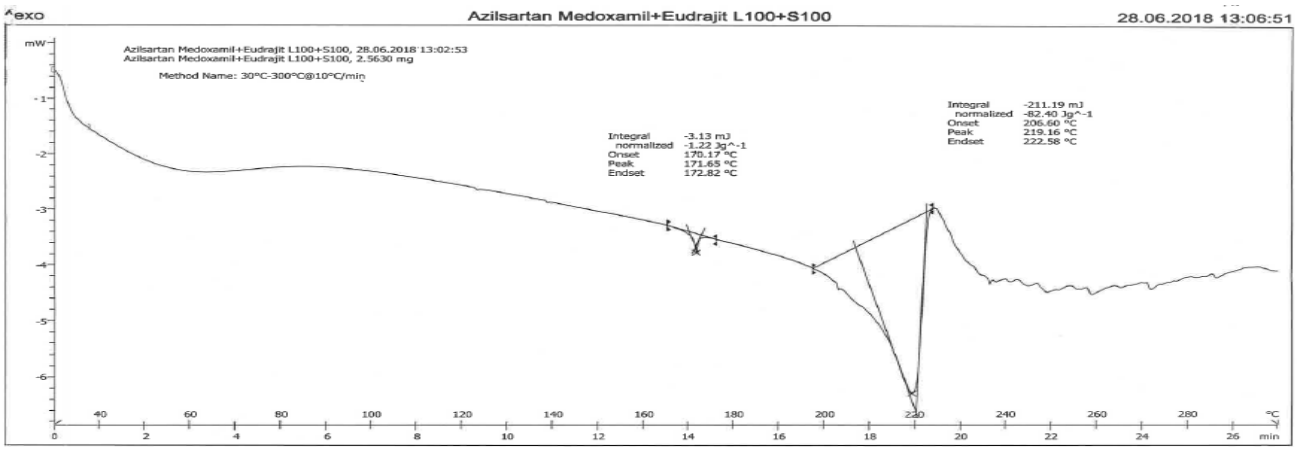


Figure 2: DSC spectrum of Azilsartan Medoxamil+ Eudragit (L-100 and S-100)

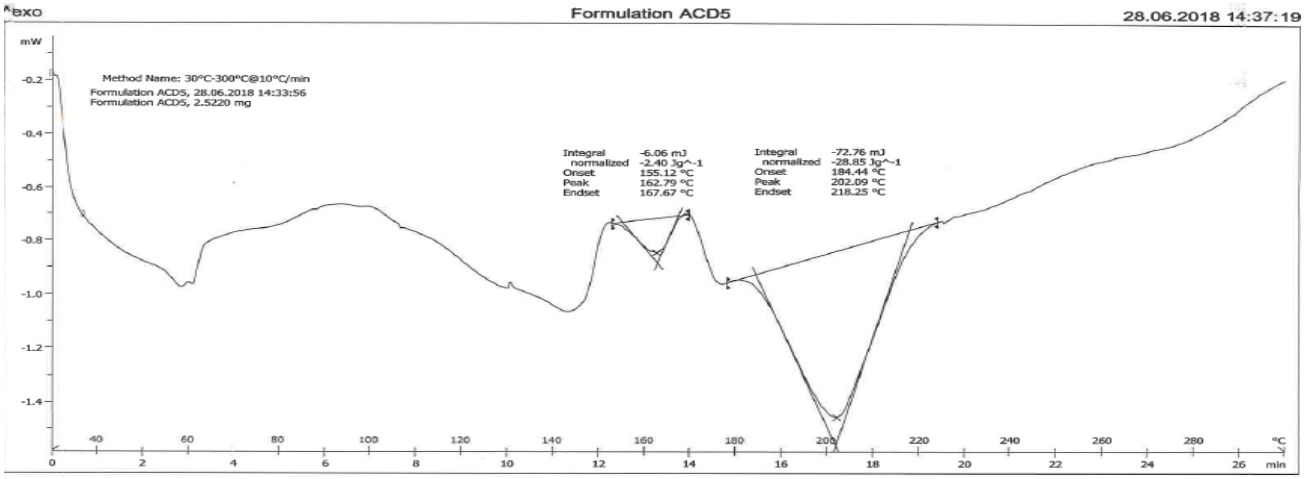


Figure 3: DSC spectrum of Azilsartan Medoxamil formulation AM5

Physical properties

The physical properties of colon targeted tablet of Azilsartan Medoxamil 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 6.90-7.00 mm. The hardness for various formulations was found to be between 4.9 to 6.4 kg/cm^2, 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 to101.76± 0.44 % which is within acceptable limits.

Table 2: Physicochemical parameters of developed colon targeted tablets of Azilsartan Medoxamil

Parameters	AM-1	AM-2	AM-3	AM-4	AM-5
Hardness (Kg/cm2)	6.4± 0.65	6.2± 0.24	5.8± 0.72	5.6± 0.26	4.9± 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**

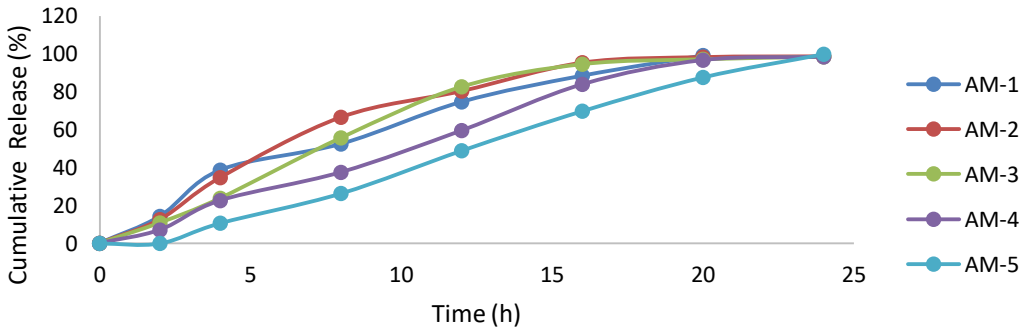
The cumulative percentage releases of different formulation of Azilsartan Medoxamil colon targeted tablets were shown in Table 3 and Figure 4.The release of Azilsartan Medoxamil from colon targeted tablets varied according to the types and proportion of polymers

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, AM47.04 in 2 hrs and 98.37 in 24 hrs. The results of cumulative drug release of CTTDS formulations from AM1 to AM5 are shown in Figure 4. CTTDS tablets of AM2 to AM5 from 98.66%, 98.45%, 98.37% and 99.79%, respectively, of their azilsartan medoxamil 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=13.94). CTTDS Formulations of azilsartan medoxamil from AM1 to AM5, containing HPMC K100M coated with Eudragit L100 along with Edragit S 100, successfully released < 90% at the end of 20 hours except AM5. Formulations were impermeable, may be due to reduced water penetration in the matrix. At the end of 2 hours drug released from AM1 to AM5 were 14.45%, 12.56%, 10.78%, 7.04% and 0.0% whereas at the end of 24 h drug release from AM2 to AM5 was found to be 98.66%, 98.45%, 98.37% and 99.79%, respectively. Formulation AM1 was failed release > 90% at the end of 24 hours. The differences between 12 hours release values for AM2, AM3, AM4 and AM5 were significant at P< 0.01 (DF=2, F= 110). Significant differences were observed between 24 hours release values (P<0.001, DF=2 and F=95). Incorporation of higher amount of HPMC K100M in all the four formulations (AM2, AM3, AM4 and AM5) was found to be more suitable to give good drug release characteristics and AM5 was found be very good release.

Table 3: 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

Figure 4. In vitro drug release study of different formulation of Azilsartan Medoxamil colon targeted Tablets



In-Vitro Release Kinetic For the Formulation (Am1 to Am5) of Azilsartan Medoxamil.

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 Korsemeyer – 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 4. While the data were plotted in graph according to a first-order of reaction equation, the formulations from AM2 to AM5 have shown a good linearity to their regression values 0.906, 0.966, 0.890 and 0.972, respectively. The best fit with higher correlation (R^2> 0.87) was found with the Korsemeyer – Peppas for AM2, AM3 and AM5 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 HPMC K100M coated with Eudragit L100 and Edragit S 100. The release profiles of AM3, AM4 and AM5 might be well clarified by Higuchi model, as the plots showed good linearity and correlation coefficient (R^2) values 0.883, 0.915 and 0.956 respectively. The diffusion mechanism of drug release was further confirmed by Korsmeyer – Peppas plots that showed good linearity (R^2 values between 0.96 and 0.98), with slope > 0.7, indicating that drug release mechanism from the formulations were non-fickian diffusion mechanism[18, 19].

Table 4: *In-vitro* release kinetics for proposed formulation (AM1 to AM5) of Azilsartan Medoxamil 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
AM1	0.042	0.849	0.074	0.046	0.913	0.700
AM2	0.852	0.906	0.801	0.812	0.966	0.722
AM3	0.873	0.966	0.870	0.883	0.984	0.748
AM4	0.965	0.890	0.854	0.915	0.963	0.619
AM5	0.995	0.972	0.888	0.956	0.980	0.771

CONCLUSION

Azilsartan Medoxamil colon targeted different formulations were developed by using release rate controlling polymers like HPMC K100M by wet granulation methods and then the tablets were enteric coated with Eudragit polymers (L-100 and S-100; 1:1) polymers. The reproducible results obtained the complete release of drug, may be the coating of certain fraction of drug by HPMC K100M coated with Eudragit L100 and Edragit S 100. 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 of the drug as well as its half life.

REFERENCES

1. Rubinstein A. Colonic drug delivery. Drug Discovery Today: Technologies. 2(1), 2005, 33-7.
2. Van den Mooter G, Kinget R., Oral colon-specific drug delivery: a review, *Drug Deliv*, 1995, 2, 81-93.
3. Ashford M, Fell J.T, Targeting drugs to the colon: delivery systems for oral administration, *J Drug Target,* 2, 1994, 241-258.
4. Devereux J.E, Newton J.M, Short M.B, The influence of density on the gastrointestinal transit of pellets, *J Pharm Pharmacol*, 42, 1990, 500-501.
5. Hunter E, Fell J.T, Sharma H, The gastric emptying of pellets contained in hard gelatin capsules, *Drug Dev Ind Pharm*, 8, 1982, 751-757.
6. Luppi B, Bigucci F, Cerchiara T, Mandrioli R, Di-Pietra AM, Zecchi V. New sensitive environmental system for colon-specific delivery of peptidic drugs. Int J Pharm, 358, 2008, 44-49.
7. Aurora J, Talwar N, Pathak V. Colonic drug delivery challenges and opportunities-an overview. Eur Gastro Rev, 2006, 1-6.
8. Watts P, Illum L. Colonic drug delivery. Drug Dev Ind Pharm. 23, 1997, 893913
9. Yang L, Chu JS, Fix JA. Colon-specific drug delivery: new approaches and *in vitro/in vivo* evaluation. Int J Pharm. 235(1-2), 2002, 1-15.
10. Cheng G, An F, Zou MJ, Sun J, Hao , He YX. Time- and pHdependent colon-specific drug delivery for orally administered diclofenac sodium and 5-aminosalicylic acid. World J. Gastroenterol. 10, 2004, 1769- 1774.
11. Hausner HH. Friction conditions in a mass of metal powder. Int.J. Metall. 3, 1967, 7-13.
12. Carr RL. Evaluating flow properties of solids. Chem. Eng. 72, 1965, 163-168.
13. Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, Vol. II Delhi: Controller of Publications, 1996.
14. Higuchi, T. Mechanism of sustained release medication:theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.*, 1963, v.52, 1145-1149.
15. Hixson AW and Crowell JH. Dependence of reaction velocity upon surface and agitation: I-Theoretical consideration. *Ind. Eng. Chem.* 23, 1931, 923-931.
16. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA.Mechanisms of solute release from porous hydrophilic polymers. Int. J.Pharm. 15, 1983, 25-35.
17. Dorozynski P, Jachowicz R, Jasinski A, Kulinowski P,Kwiecinski S, Skorka T,Szybinski K. The polymers for the preparation of hydrodynamically balanced systems: methods of evaluation. *Drug Dev.Ind. Pharm*. 9, 2004, 947–957.
18. Subhash Chandra Bose, P, Srikanth Reddy, P, Valluru Ravi, Sarita, D, and Pramod Kumar, TM. Formulation and evaluation of sustained release floating tablets of diltiazem Hcl using xanthan gum. RJPBCS, 2(2), 2011, 319 – 328.
19. Apurba Sarker Apu, Fahmida Nashid Afroza, Hossain Md. Mohiuddin, Kanij Fatema, Md. Zakiur Rahman, Md. Amran Howlader. Design, Development and In Vitro Evaluation of Diclofenac Sodium Matrix Tablet Prepared by Direct Compression Using Methocel K100LV CR Polymer. Int J Pharmaceu Sci Rev Res, 13(2), 2012, 121 – 127.

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