www.ijarp.com ISSN 2456-9992 Page: 01-23

International Journal Advanced Research Publications

Research Article

Volume: 02
Issue: 07

FORMULATION AND OPTIMIZATION OF CONTROLLED-RELEASE MATRIX TABLETS OF AZILSARTAN MEDOXOMIL USING NATURAL AND SYNTHETIC HYDROPHILIC POLYMERS

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Article Received: 20 June 2026, Article Revised: 10 July 2026, Published on: 30 July 2026

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Doi: https://doi-doi.org/101555/ijarp.6148

ABSTRACT

The present study aimed to formulate and optimize controlled-release matrix tablets of Azilsartan Medoxomil using natural and synthetic hydrophilic polymers to achieve sustained drug release over 24 hours. Preformulation studies, including organoleptic properties, angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, and compressibility index, confirmed that the drug possessed satisfactory flow and compression characteristics. Fourier Transform Infrared (FTIR) spectroscopy demonstrated the compatibility of Azilsartan Medoxomil with the selected polymers by showing no significant drug–polymer interactions. Matrix tablets were prepared using Hydroxypropyl Methylcellulose (HPMC K100M) and Xanthan Gum individually and in combination by direct compression. The formulated tablets were evaluated for physicochemical properties, including hardness, friability, weight variation, drug content, and in vitro dissolution. All formulations complied with pharmacopoeia specifications, with drug content ranging from 93% to 100%. Dissolution studies performed in a pH 1.2 acid buffer followed by a pH 6.8 phosphate buffer demonstrated that Xanthan Gum alone exhibited a comparatively faster release, whereas the combination of HPMC K100M and Xanthan Gum effectively sustained drug release. Among all formulations, batch F9 showed the optimum performance with 99.74% cumulative drug release over 24 hours. Release kinetic analysis revealed that the optimized formulation followed zero-order kinetics (R^2 = 0.993) with anomalous (non-Fickian) diffusion as the predominant release mechanism. Accelerated stability studies conducted for three months confirmed the stability of the optimized formulation without significant changes in its

physicochemical properties or dissolution profile. The study concludes that formulation F9 is a promising controlled-release matrix tablet of Azilsartan Medoxomil capable of providing sustained drug release for 24 hours, thereby offering potential benefits in improving therapeutic efficacy and patient compliance. Further in vivo studies are recommended to validate its clinical performance.

KEYWORDS: Azilsartan Medoxomil; Controlled-release matrix tablets; HPMC K100M; Xanthan Gum; Hydrophilic polymers; Direct compression; In vitro drug release; Zero-order kinetics; Non-Fickian diffusion; Stability studies.

INTRODUCTION

The objective of any drug delivery system is to provide a therapeutic amountof drug to the targeted site in the body to achieve the desired therapeutic effect. In recent years, attention has been focused on the development of new drug delivery systems rather than the invention of new molecules. Because the development cost for a new drug molecule is very high and possibility of repurposing successful drugs by applying concepts and techniques of controlled release drug delivery systems.

CONVENTIONAL DRUG DELIVERY SYSTEM

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms.

The oral dosage form has survived due to

1. Relatively simple and inexpensive to make
2. Convenient for the patient
3. Technology is easy to adapt to the changing needs of the drug substance
4. Simplifies the regulatory approval process.

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for the immediate release of drug for rapid or immediate absorption[1].

Controlled Drug Delivery[1]

For many drugs, the basic goal of therapy is to achieve a steady state blood or tissue level i.e., therapeutically effective and non toxic, for an extended period of time. For this purpose

controlled release dosage forms are designed. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release depot and repository dosage forms are terms used for identifying drug delivery systems, which achieve prolonged therapeutic effect by continuous release of drug for extended time after single dose administration. controlled release systems release drug at predetermined rate and sustained release systems only prolong the drug release.

Oral Controlled Drug Delivery System[4]

Oral route has been commonly adopted and most convenient route for the drug delivery, as the patient acceptance for oral route is high. It is relatively safe route of administration than most parenteral routes where the constraints of sterility and potential damage at site of administration are minimal. Controlled release preparation release the drug in controlled manner in gastrointestinal tract for systemic uptake.

As there is more flexibility and received more attention in designing of dosage form for oral route than drug delivery design for other routes. Oral controlled delivery systems can be broadly classified into following categories, depending on their mechanism of drug release

1. Dissolution – controlled release
a. Encapsulation dissolution control.
b. Matrix Dissolution control.
2. Diffusion Controlled Release
a. Reservoir devices
b. Matrix devices
3. Water penetration Controlled
a. Osmotically controlled release
b. Swelling Systems.
4. Ion exchange resins
5. Gastro retentive Systems
6. Bio adhesive drug delivery systems.
7. Microspheres.
8. Spheronization/ Pelletization
9. Coating Technologies.

Dissolution Controlled Release System[5]

This can be obtained by slowing the dissolution rate of the drug. Slowing of dissolution rate can be achieved by incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. Also the drug may be incorporated in hydrophobic or hydrophilic matrix. The rate of penetration of dissolution fluid into matrix controls the rate of drug availability. Also the porosity of compressed structure is important parameter.

Matrix Formulations[6]

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipients in order to achieve release by a continuous leaching of the drug from the inert matrix core.

Matrix systems can be divided into three types

1. Monolithic matrix tablets
2. Gel forming hydrophilic matrix tablets
3. Erodable (hydrophobic) matrix tablets

Inert monolithic matrix tablets

Probably the simplest method of obtaining controlled release of a drug from an oral dosage form is incorporation of a drug in an inert matrix. In this inert means non interacting with the biological fluids. The main reason for its popularity is that drug release from plastic matrix tablets is independent on the state and condition of the digestive juices, which may show large inter and intra patient variability (pH, viscosity).

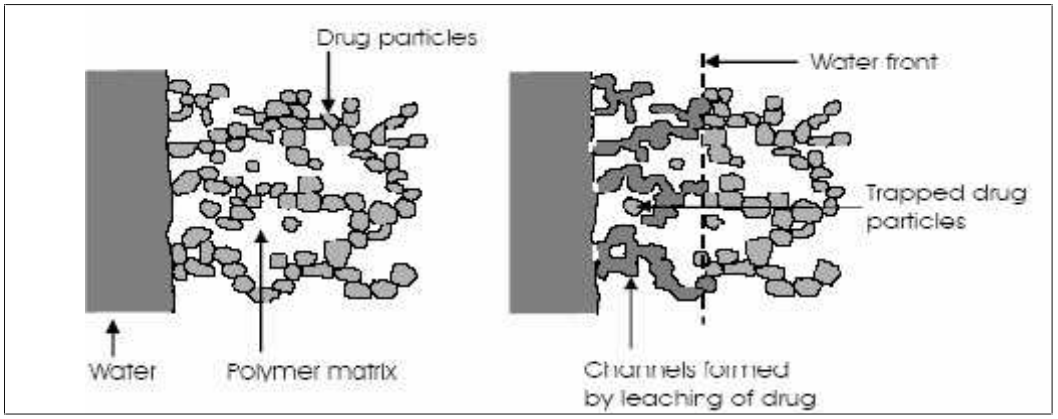
During its transit through the gastro-intestinal tract, the porous matrix tablet does not disintegrate like conventional tablets, but remains intact and the skeleton can be recovered in faeces. The materials used in the preparation of these inert matrices are predominantly (insoluble) polymers and lipophilic compounds. The first polymers to be used for the preparation of matrix tablets were (semi- synthetic polymers such as polyethylene, poly vinyl chloride, poly methyl methacrylate, polystyrene, poly vinyl acetate, cellulose acetate and ethyl cellulose. The fat compounds used included carnauba wax, hydrogenated castor oil, and tri stearin.

Major drawback of most of the inert polymeric matrix tablets were their inherent first order drug release characteristics, their poor direct compression characteristics and the problem leaning of agglomeration equipment used for the preparation of agglomerates with the required compression characteristics.

Mechanism of release of inert monolithic matrix tablets

Release from inert matrix tablets occurs via a leaching mechanism. Drug particles dispersed in the polymer matrix dissolve in the penetrating gastrointestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that created by the dissolution of the drug particles. At drug loadings exceeding approximately 10-15 % volume, a continuousstructure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release.

Schematically representation of a leaching-based release mechanism.



Solvent activated matrix tablets

The use of solvent-activated matrix tablets as a method to obtain zero order release i.e. constant release rates over an extended period was first proposed by Hopfenberg. Solvent-activated drug delivery system is a collective term comprising those systems in which the interact ion between polymer and water is responsible for achieving controlled release. The interaction with water may include plasticization, swelling, dissolution, erosion or degradation of the polymer. The two most important types of solvent activated matrix tablets are gel-forming hydrophilic matrix tablets and erodible (hydrophobic) matrix tablets.

Gel-forming hydrophilic matrix tablets

Gel-forming hydrophilic or swellable matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swellable hydrophilic polymer. These systems have been widely studied by researchers since they offerthe possibility to obtain a constant drug delivery over an extended period of time. Drug release is a function of the polymer

characteristics. Upon swallowing gel-forming hydrophilic matrix tablets, the hydrophilic polymer is plasticized by the aqueous gastro-intestinal due to which undergoes macromolecular chain relaxation and volume expansion. Consequently, upon penetration of the gastro-intestinal fluids into tablet, a sharp front can be distinguished which separates a dry, glassy core from a hydrated and rubbery gel layer. Release is governed by diffusion of the dissolved drug through the swollen gel layer and generally shows a burst effect, caused by dissolution and leaching of drug particles present at the surface prior to formation of the release-controlling gel. Other swellable polymers, which have been applied in swelling-controlled oral drug delivery systems, which show solvent controlled release, are guar gums, xanthan gum, poly (ethylene oxide) (PEO), poly (vinyl alcohol), ethylene-vinyl alcohol copolymers (EVA) and dextrans.

Water Penetration Controlled Release System

In these systems, control release is obtained by the penetration of water into the system. There are following types of water penetration-controlled release system,

Osmotically Controlled Release System

In this system delivery of drug is controlled by solvent influx across a semi permeable membrane which carries the drug outside through a laser drilled orifice. The osmotic and hydrostatic pressure differences on either side of semi permeable membrane causes fluid transport into the system, so the rate of drug release is dependent on osmotic pressure of formulation.

METHODOLOGY

PRE-FORMULATION STUDIES

Pre-formulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the pre-formulation phase begins early in the discovery process such the appropriate physical, chemical data is available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered in the present study.

The following pre-formulation studies were performed

- ✓ Study of organoleptic properties
- ✓ Solubility analysis

- ✓ Melting point of drug
- ✓ Drug powder characterization
- ✓ Drug-excipients compatibility study by FT-IR[24]

Organoleptic properties

The Organoleptic character of the drug like colour, odour, taste and appearance play an important role in the identification of the sample and hence they should be recorded in an descriptive terminology.

1. Solubility studies
2. Melting point
3. Loss on drying
4. Drug powder characterization[25]
5. Angle of repose
6. Bulk density
7. Tapped Density

Drug-Excipient Compatibility Studies

Fourier Transform Infrared (FTIR) Spectroscopy

FT-IR spectra of pure drug, Pure HPMC K100 M, Pure Xanthan Gum & physical mixtures of this polymer with drug were recorded on Bruker alphaFT-IR spectrophotometer using KBr discs. The instrument was operated under dry air purge and the scans were collected at scanning speed 2 mm/sec with resolution of 4 cm^{-1} over the region 4000-400 cm^{-1}. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.

Construction of calibration curve

Calibrations curve of AZILSARTAN MEDOXOMIL in Acid buffer pH 1.2Preparation of 0.2 M potassium chloride

0.2 M Potassium Chloride was prepared according to IP 1996. A quantity of 14.9 gm of potassium chloride was dissolved in water and made up the volume to1000 ml using water.

Preparation of 0.2M HCl

0.2 M HCl prepared by diluting 17ml of Conc. HCl in to water and made upthe volume to 1000ml using water.

Preparation of Acid buffer pH 1.2

The Acid buffer pH 1.2 prepared according to IP 1996 by mixing the 50ml of 0.2 M potassium chloride and 85 ml of 0.2 M HCl and made up the volume to200ml using water.

Scanning of AZILSARTAN MEDOXOMIL in Acid buffer pH 1.2

The absorption maxima of the standard solution were scanned between 200- 400 nm on Lab India 3000 UV-Vissible spectrophotometer. The absorption maxima were found at 216 nm.

Procedure

An accurately weighed quantity of AZILSARTAN MEDOXOMIL was dissolved in an amount of methanol not exceeding 2% of final volume and diluted quantitatively with Acid buffer pH 1.2 to obtain a solution having known concentration(4, 8, 12, 16, 20, 24, 28 and 32 µg/ml). Absorbance of AZILSARTAN MEDOXOMIL determined at 216 nm.

Calibration curve of AZILSARTAN MEDOXOMIL in phosphate buffer pH 6.8

Preparation of 0.2 M potassium dihydrogen phosphate

0.2 M potassium dihydrogen phosphate was prepared according to IP 1996. A quantity of 27.2 grams of potassium dihydrogen phosphate was dissolved in water and made up the volume to 1000ml using water.

Preparation of 0.2 M NaOH

0.2 M NaOH prepared by dissolving 8 gms of NaOH in to water and madeup the volume to 1000ml using water.

Preparation of phosphate buffer pH 6.8

The phosphate buffer pH 6.4 prepared according to IP 1996 by mixing the 50ml of 0.2 M potassium dihydrogen phosphate and 39.1ml of 0.2 M NaOH and make up the volume to 200ml using water.

Scanning of AZILSARTAN MEDOXOMIL in phosphate buffer pH 6.8

The absorption maxima of the standard solution were scanned between 200- 400 nm on Lab India 3000 UV-Vissible spectrophotometer. The absorption maxima were found to 216 nm.

Procedure

An accurately weighed quantity of AZILSARTAN MEDOXOMIL was dissolved in phosphate buffer pH 6.8 to obtain a solution having known concentration (4, 8, 12, 16, 20,

24, 28 and 32 µg/ml). The absorbance of AZILSARTAN MEDOXOMIL was determined at 216 nm.

Formulation of controlled release matrix tablets of AZILSARTAN MEDOXOMIL by the direct compression method

The key ingredients included in the formulation are Hydrophilic polymers: Xanthan gum and HPMC K100M Filler: MCC

Anti-adherent: Talc

Lubricant: Magnesium Stearate

Binder: PVP

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically to this required quantity of AZILSARTAN MEDOXOMIL was added and mixed with the help of pestle. The powder blend was then lubricated withmagnesium stearate and talc mixed for about 3 minutes. Compression operation was carried on rotary tablet compression machine fitted with 6 mm round shaped, standard flat face punch sets having plain on both sides at average weight 100 mg/tab. Before going to compression powder blend was evaluated for all physical parameters like angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio.

Formula of Controlled release matrix tablets of AZILSARTAN MEDOXOMIL

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Azilsartan Medoxomil	4	4	4	4	4	4	4	4	4	4	4	4
HPMC K100M	30	35	40	-	-	-	15	20	20	0	20	0
Xanthan gum	-	-	-	30	35	40	20	15	20	20	0	0
PVP	5	5	5	5	5	5	5	5	5	5	5	5
MCC	59	54	49	59	54	49	54	54	49	49	49	49
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Mg. stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total wt (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Formulation of AZILSARTAN MEDOXOMIL controlled release matrix tablet

Evaluation of Controlled Release Tablets of Azilsartan Medoxomil: The prepared controlled release tablets were evaluated for their physicochemical properties, including tablet thickness, diameter, hardness, friability, weight variation, and drug content uniformity,

according to Indian Pharmacopoeial specifications. In vitro dissolution studies were performed using USP Type II (paddle) dissolution apparatus at 50 rpm in 900 mL dissolution medium maintained at 37 ± 0.5°C, employing pH 1.2 acidic buffer for the initial 2 hours followed by pH 6.8 phosphate buffer for the remaining 22 hours. Samples were collected at predetermined intervals, analyzed by UV spectrophotometry at 216 nm, and the cumulative drug release data were used to evaluate the release kinetics by fitting to Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models to determine the drug release mechanism. The optimized formulation was further subjected to accelerated stability studies as per ICH guidelines at 40 ± 2°C/75 ± 5% RH for 3 months, and periodically evaluated for physical characteristics, drug content, and dissolution behavior.

RESULT AND DISCUSSION

PRE-FORMULATION STUDIES

Physical characteristics of a drug

Physical characteristics of the drug (AZILSARTAN MEDOXOMIL)

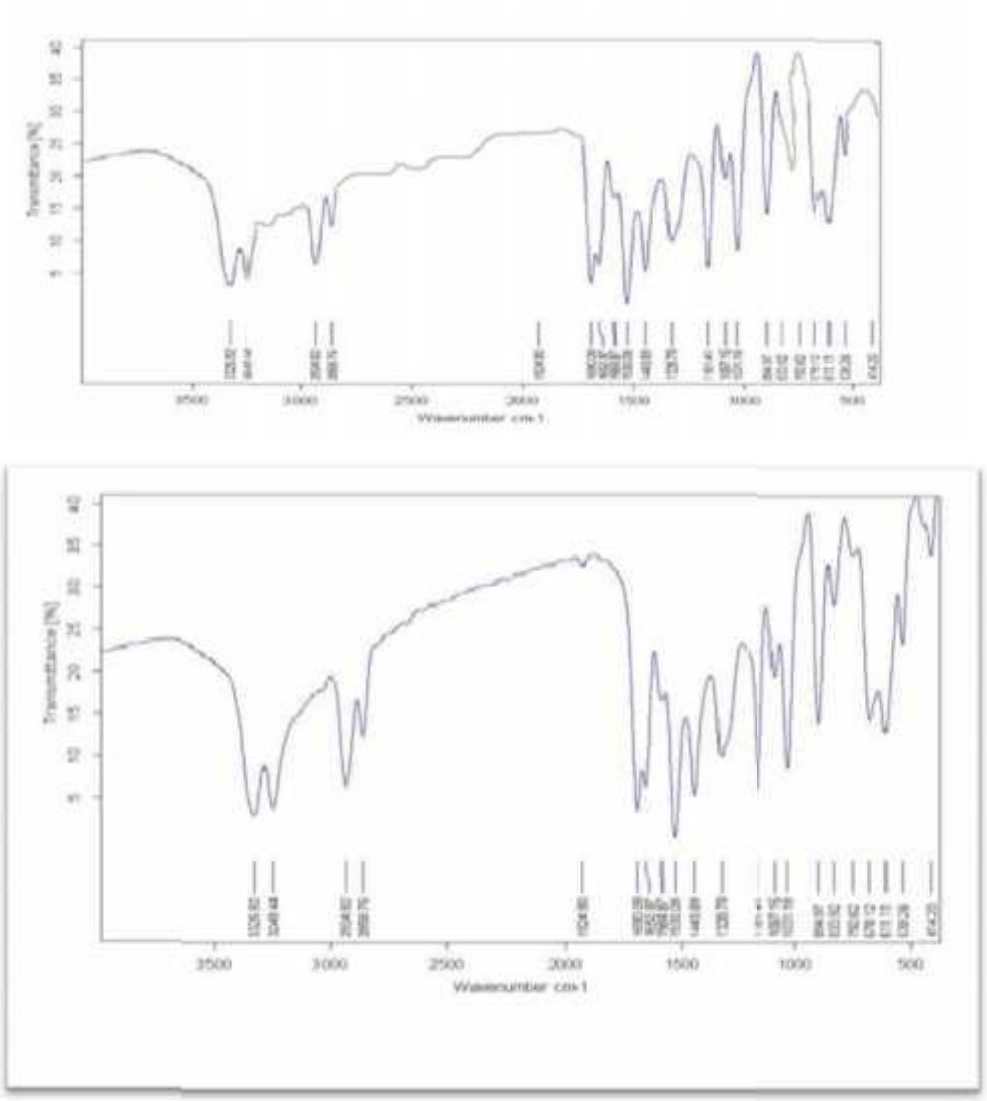
S. No	Parameter	Specifications
1	Loss on Drying (%)	0.40
2	Bulk density (g/ml)	0.415
3	Tapped Density (g/ml)	0.498
4	Hausner's ratio	1.26
4	Compressibility index (%)	<15
5	Angle of repose (□ ')	24.11°

All the powder characteristics were good and satisfied according to the pharmacopeia.

FTIR Studies

Potential chemical interactions between the drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibilities of chemical interaction between drug and excipients. FTIR spectra of pure drug and optimized formulations were analyzed over the range 400-4000cm^{-1}. Compatibility studies were performed using FT-IR Spectrophotometer. The FT-IR spectrum of pure AZILSARTAN MEDOXOMIL drug was compared with FT-IR spectrum of physical mixture of AZILSARTAN MEDOXOMIL (AZILSARTAN MEDOXOMIL, HPMC K100 M, Xanthan gum, MCC, PVP, Talc and Mg.sterate). The spectra for all formulations are shown belowfigure no 4 to 9.

FTIR spectra of AZILSARTAN MEDOXOMIL



FTIR spectra of Drug with excipients.

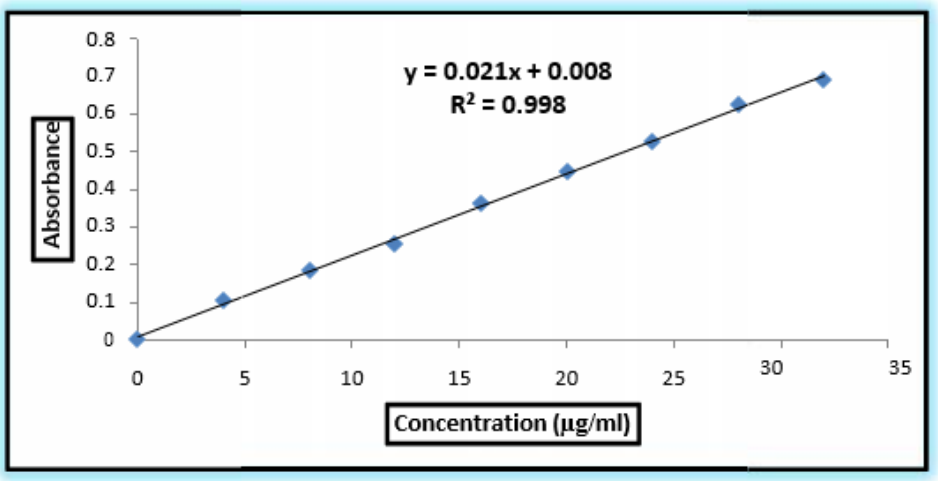
FT-IR Peaks of various compounds

Wave numberin cm^{-1}	**Functional groups**	**Pure drug AZILSARTAN MEDOXOMIL**	**Physicalmixture**
1210-1150	C-N Stretching	1151.2 cm^{-1}	1152.4 cm^{-1}
1360-1180	C-NH_2 Stretching	1306.1 cm^{-1}	1307.5 cm^{-1}
1900-1600	C=O Stretching	1800.8 cm^{-1}	1800.8 cm^{-1}
2990-2850	C-CH_3 Stretching	2984.9 cm^{-1}	2983.2 cm^{-1}
3490-3300	N-H Stretching	3305.9 cm^{-1}	3306.7 cm^{-1}

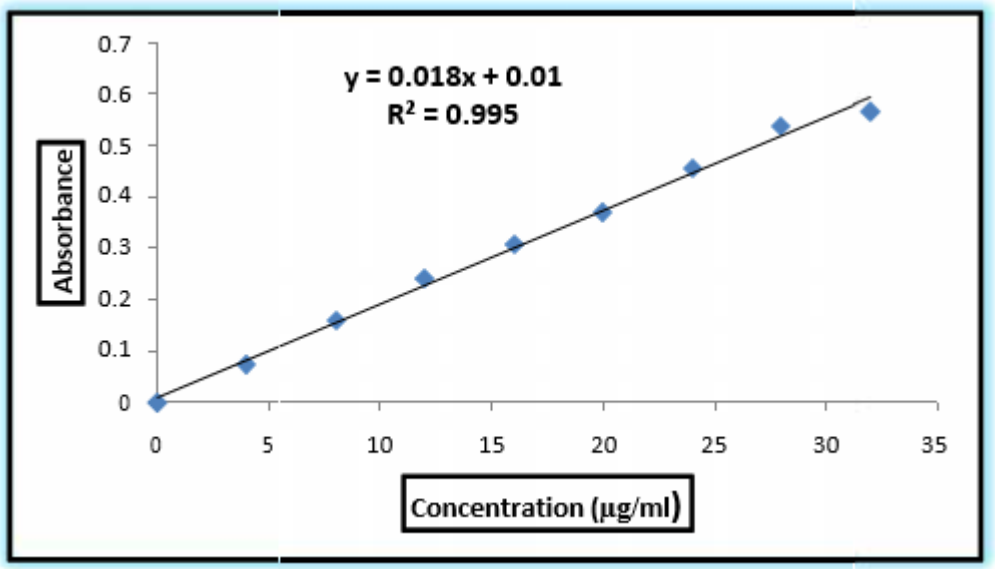
The FTIR spectrum analysis showed that there is no appearance or disappearance of any characteristic peaks of pure AZILSARTAN MEDOXOMIL and in the physical mixture of drug with polymer and excipients. The presence of peaks at the expected range confirms that the materials taken for the study are genuine. Due to stretching C-N, C-NH_2, C=O, C-CH_3 and N-H respectively in optimized formulations also these peaks were well preserved with

additional peaks which correspond to the excipients used in the formulation. This indicated that no drug excipients interaction.

Calibration curve of AZILSARTAN MEDOXOMIL



Calibration curve Graph in pH 1.2 Acid Buffer



Calibration curve Graph in PH 6.8 Phosphate Buffer.

Evaluation of pre compression parameters

Powder characterization of formulations

Formulation code	Angle of Repose (± SD)	BD (gm/ml) (± SD)	TD (gm/ml)(± SD)	Carr's index (%) (± SD)	Hausner'sratio (± SD)
F1	23.03±0.04	0.412±0.02	0.477±0.02	14.92±0.05	1.18±0.05

F2	20.85±0.01	0.407±0.03	0.486±0.01	14.91±0.07	1.19±0.04
F3	20.85±0.04	0.410±0.06	0.481±0.01	13.93±0.04	1.21±0.02
F4	22.30±0.07	0.398±0.04	0.491±0.07	14.72±0.01	1.19±0.06
F5	19.98±0.09	0.396±0.03	0.480±0.03	13.12±0.03	1.16±0.03
F6	22.06±0.06	0.412±0.01	0.489±0.01	14.27±0.01	1.15±0.01
F7	23.19±0.03	0.409±0.04	0.472±0.02	13.56±0.04	1.16±0.03
F8	22.05±0.09	0.401±0.05	0.492±0.03	12.91±0.07	1.17±0.05
F9	24.11±0.03	0.415±0.01	0.498±0.04	15.00±0.06	1.26±0.04

(n=3±S.D) (S.D=Standard deviation)

For the powder blend of all the formulated batches, the angle of repose was found to be in the range of 19° to 24°, thus indicating that the flow properties were excellent. Hausner's ratio was less than 1.20 for all the batches indicating good flowproperties. Formulation from F10 to F12 doesn't give good shape and the formation of tablet also is not possible. So, no further parameters are able to be carried for these formulations from F9 to F12.

Evaluation of AZILSARTAN MEDOXOMIL tablets

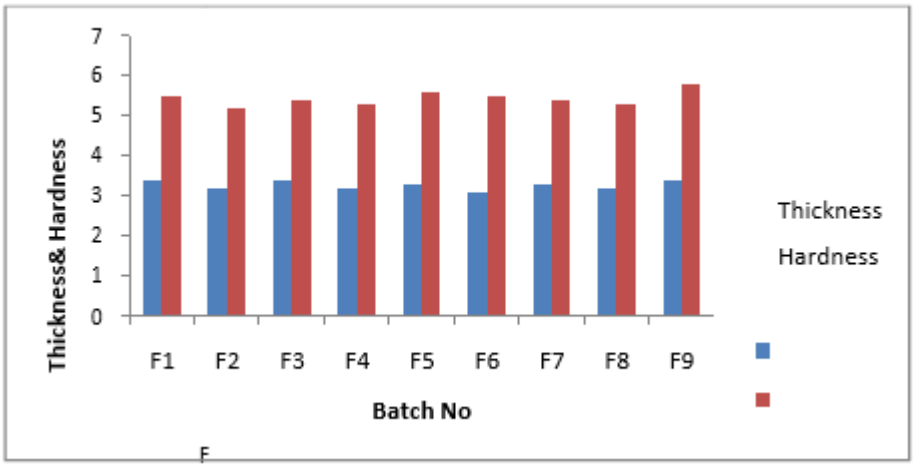
Evaluation of Physical Characteristics of controlled release matrix tablets of AZILSARTAN MEDOXOMIL

Formulation code	**Weight variation (mg) (±SD)**	**Hardness (kg/cm^2) (±SD)**	**Thickness (mm) (± SD)**	**Drug content (mg)(± SD**	**Friability %**
F1	100.4±1.24	4.93±0.23	3.009±0.02	93.76±0.19	0.30
F2	100.9±1.61	4.13±0.30	3.009±0.02	98.16±0.27	0.40
F3	100.4±1.56	3.73±0.11	3.008±0.02	89.87±0.41	0.16
F4	100.3±1.28	3.93±0.23	3.009±0.02	97.28±0.33	0.40
F5	100.8±1.16	4.13±0.15	3.008±0.02	93.48±0.26	0.60
F6	100.0±1.42	4.4±0.2	3.010±0.0	95.67±0.17	0.60
F7	100.8±1.00	4.0±0.2	3.009±0.02	93.87±0.32	0.50
F8	100.8±1.28	3.53±0.11	3.009±0.02	88.92±0.21	0.51
F9	100.3±1.04	4.0±0.115	3.009±0.02	97.87±0.16	0.57

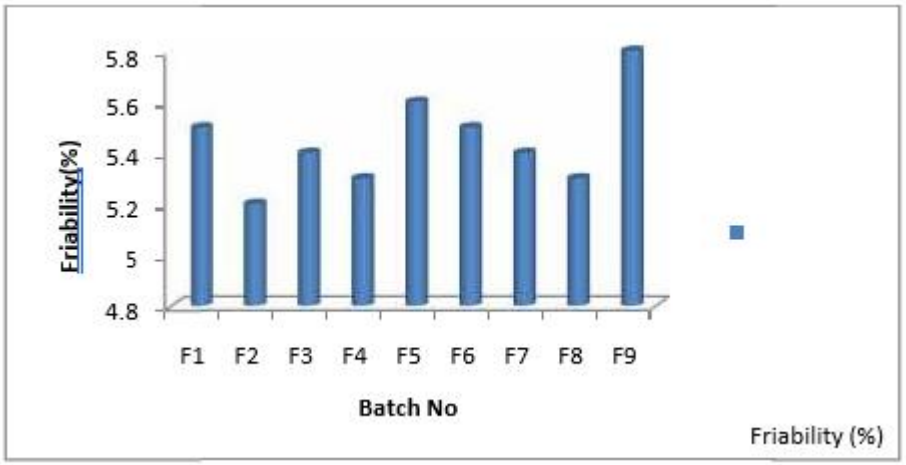
(n=3±S.D) (S.D=Standard deviation)

The histograms of hardness, thickness, weight variation, friability and drug content was mentioned in figure.

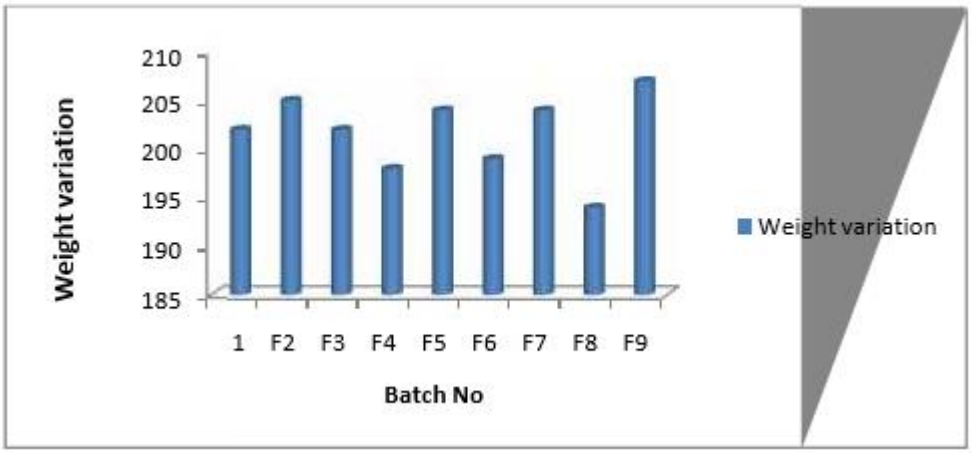
Thickness and Hardness of AZILSARTAN MEDOXOMIL tablets



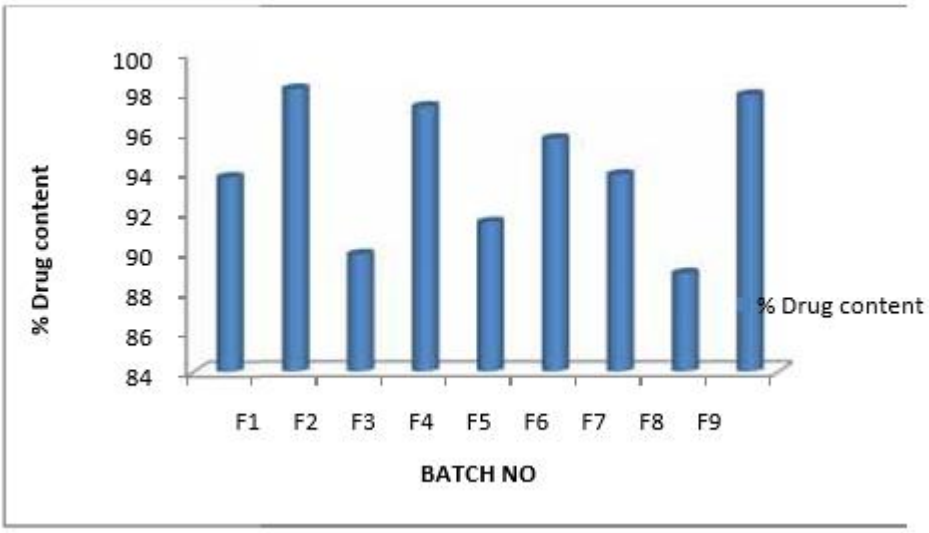
Friability of AZILSARTAN MEDOXOMIL tablets



Weight variation of AZILSARTAN MEDOXOMIL tablets



% Drug Content of AZILSARTAN MEDOXOMIL tablets



The formulated tablets (F1–F9) exhibited satisfactory physicochemical characteristics, with weight variation within pharmacopoeial limits. Tablet thickness ranged from 3.008–3.010 mm, diameter from 6.008–6.010 mm, hardness from 3.53–4.13 kg/cm², friability from 0.16–0.60%, and drug content from 93–100%. Overall, all formulations complied with pharmacopoeial specifications for physical quality parameters, indicating good tablet quality and uniformity.

INVITRO DRUG RELEASE STUDY

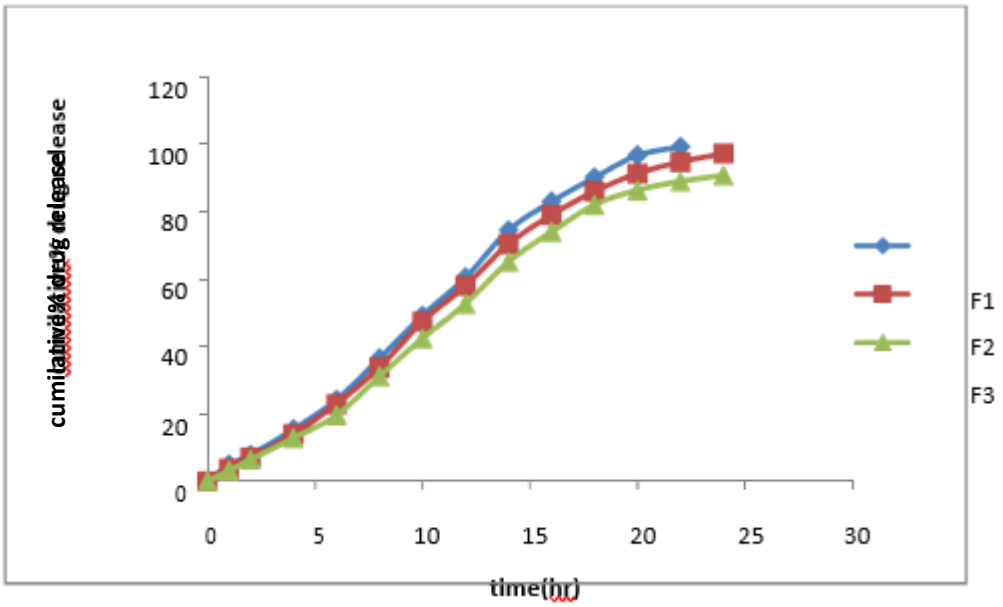
The dissolution studies of the formulation (F_1 to F_9) were carried out in USP dissolution apparatus (paddle) in 900 ml of 0.1N HCL of pH 1.2 for 2 hr and phosphate buffer pH 6.8 for remained 22 hr as dissolution medium. The results of the dissolution study depend on polymer concentration.

Cumulative Percentage drug release of formulations withHPMC K100M (F_1-F_3)

Time (hr)	Cumulative % drug releaseF_1	Cumulative % drug releaseF_2	Cumulative % drug releaseF_3
0	0	0	0
1	4.98	3.64	3.15
2	7.86	6.99	6.42
4	15.46	13.98	12.87
6	24.19	22.89	19.65
8	36.47	33.75	31.16
10	49.19	47.39	42.41
12	60.46	57.97	52.65
14	74.49	70.38	65.11
16	83.78	79.13	74.42
18	90.19	86.72	82.21

20	96.74	91.31	86.41
22	99.24	94.74	89.63
24		97.27	90.81

Cumulative percentage drug release of formulations containingHPMC K100 M



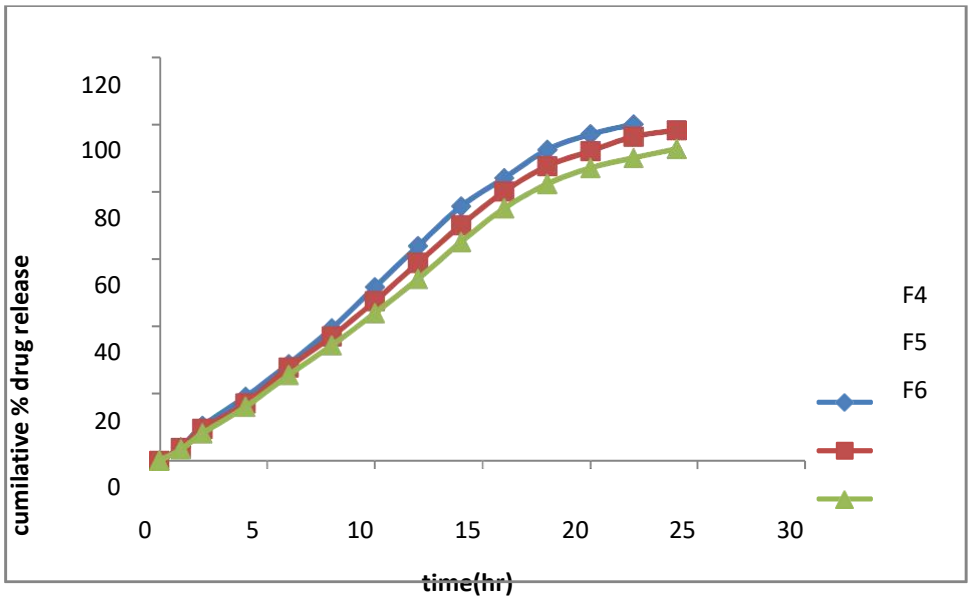
From the above figure it can be observed that the polymer HPMC K100 M has controlled effect on the release of drug from the controlled release matrix tablet. The percentage of drug release from formulations F_1, F_2 and F_3 were 99.24%, 97.27% and 90.81% respectively and difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer. The cumulative percent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented.

Cumulative Percentage drug release of formulations withXanthan gum (F_4-F_6)

Time(hr)	Cumulative % drug release F_4	Cumulative % drug releaseF_5	Cumulative % drug releaseF_6
0	0	0	0
1	3.99	3.74	3.35
2	10.31	9.45	8.12
4	19.15	17.34	16.69
6	28.76	27.68	25.42
8	39.35	36.93	34.25
10	51.59	47.41	43.85
12	63.79	58.79	54.56
14	75.59	70.63	65.42
16	84.65	80.72	75.14
18	92.41	87.52	82.24

20	97.19	92.74	87.28
22	99.98	96.27	90.71
24	-	98.15	92.64

Cumulative percentage drug release of formulations containingXanthan gum (F_4-F_6)

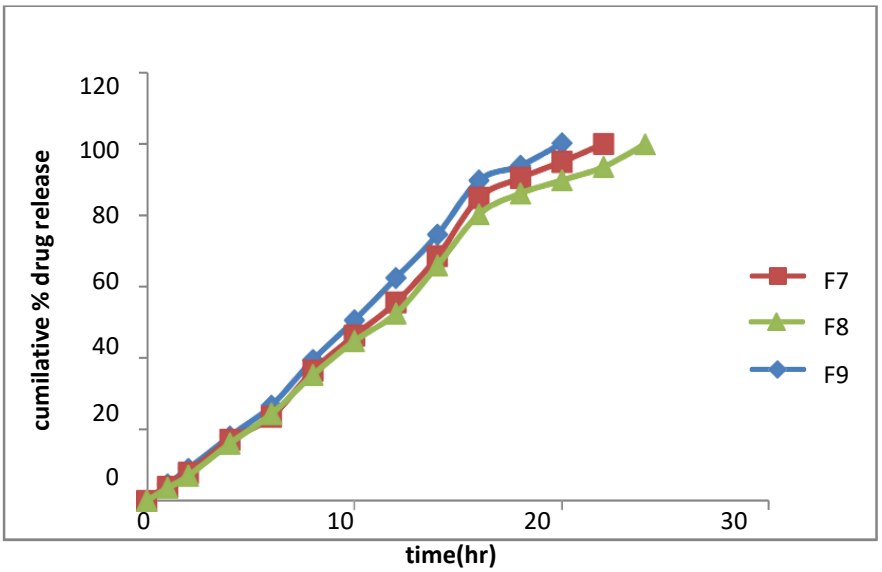


From the above figure it can be observed that the polymer xanthan gum has controlled effect on the release of drug from the controlled release matrix tablet. The percentage of drug release from formulations F_4, F_5 and F_6 was 99.98%, 98.15% and 92.64% in 24hr respectively. The difference in the drug release profile of various formulations was due to the presences of different concentrations of polymer.

Cumulative Percentage drug release of formulations with a combination of polymers (F_7-F_9)

Time(hr)	**Cumulative % drug release F_7**	**Cumulative % drug releaseF_8**	**Cumulative % drug releaseF_9**
0	0	0	0
1	4.54	3.84	3.61
2	8.99	7.78	6.99
4	18.29	17.12	16.89
6	26.61	23.45	24.31
8	39.37	36.39	35.21
10	50.45	46.19	44.68
12	62.29	55.47	52.42
14	74.42	68.36	65.85
16	89.58	84.69	80.14
18	93.69	90.27	85.97
20	99.98	94.78	89.67
22	-	99.79	93.41
24	-	-	99.74

Cumulative percentage drug release of formulations containing Combination of polymers (F_6-F_9)



From the above figure it can be observed that the polymer HPMC K100 M and Xanthan gum has controlled effect on the release of drug from the controlled release matrix tablet. The percentage of drug release from formulations F_7, F_8, and F_9 were 99.98%, 99.79%, and 99.74% in 24hr respectively. These are the formulations done by combining polymers. The cumulativepercent of drug release from various formulations and release coefficients values of the various models for respective formulation were represented. The percentage of drug release from formulations F_2, F_3, F_5, F_6 and F_9 was found to be 97.27%, 90.81%, 98.15%, 92.64% and 99.74% in 24 h respectively. The formulationsF_1, F_4, F_7 and F_8 was found to be 90.45%, 92.41%, 93.61% and 90.27% respectively. The formulations F_1, F_4, F_7 and F_8 were failed to release drug up to 24 hr and formulation with combination of polymers (HPMC K100 M & XANTHAN GUM)in 1:1 ratio was released drug 99.74% in 24 hrs. Formulation F_9 was considered as best formulation among all formulations and controlled the drug release for desired period of time (24hrs). Hence F_9 chosen for kinetic studies.

RELEASE KINETICS

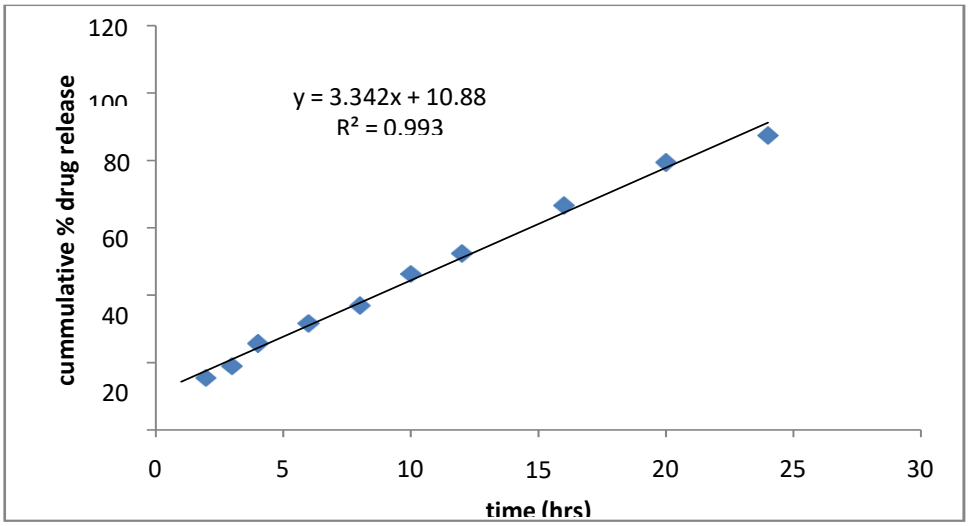
Release kinetics of the optimum formulation

Time (hr)	√T	Log T	Cumulative % drug dissolved	Cumulative % drug undissolved	Log Cumulative % drug dissolved	Log Cumulative % drug Undissolved
0	0	0	0	100	0	2
1	1	0	3.61	96.39	0.557	1.98
2	1.414	0.301	6.99	93.01	0.844	1.96

4	2.0	0.60	19.57	80.43	1.29	1.90
6	2.44	0.778	25.31	74.69	1.40	1.87
8	2.8	0.90	35.21	64.79	1.54	1.81
10	3.16	1.0	44.68	55.32	1.65	1.75
12	3.46	1.079	52.42	47.58	1.719	1.67
14	3.74	1.146	65.85	34.15	1.818	1.53
16	4.0	1.20	80.14	19.86	1.90	1.29
18	4.2	1.255	85.97	14.03	1.93	1.14
20	4.47	1.30	89.67	10.33	1.95	1.014
22	4.69	1.34	93.41	6.59	1.97	0.818
24	4.89	1.38	99.74	0.26	1.998	-0.585

To know the mechanism of drug release from these formulations, the data were treated according to zero order (cumulative amount of drug released Vs time), first-order (log cumulative percentage of drug remaining Vs time), Higuchi's (cumulative percentage of drug released Vs square root of time), and Korsmeyer (log cumulative percentage of drug released Vs log time) equations.

ZERO ORDER Plot of F_9 Formulation



Release Kinetics of AZILSARTAN MEDOXOMIL

Formulation	Zero –Order R^2	First- Order R^2	Higuchi R^2	Korsmeyer and peppas	
				R^2	N
F_9	0.993	0.738	0.9701	0.6841	0.6045

The in vitro release rate were fitted to Korsemeyer-peppas model and interpretation of release exponent value (n) enlighten in understanding the release mechanism from the dosage form. The release exponent value (n) obtained thus obtained was 0.6045. The drug release was

diffusion controlled as plot of Higuchi's model was found to be linear. The F_9 formulation exhibited anomalous (non Fickian)diffusion mechanism. These Formulations are also showed as highest R^2 values of zero order kinetics indicating the amount of drug from the matrix system were by both diffusion and erosion.

Selection of optimized batch

The F_9 of controlled release matrix tablet was chosen as optimized formulation because it showed more linearity between the cumulative percentage AZILSARTAN MEDOXOMIL versus time as indicated by the highest value of the correlation co-efficient in all selected models, among controlled release matrix tablet and best fitted for both Korsemeyer-peppas (0.6841) and zero order (0.993) model.

Summary

The present study focused on the formulation and evaluation of controlled-release matrix tablets of Azilsartan Medoxomil using HPMC K100M and Xanthan gum as release-retarding polymers. Preformulation studies confirmed that the drug possessed acceptable flow and compressibility characteristics within pharmacopoeial limits, while FTIR analysis demonstrated the absence of any drug–polymer interaction, indicating compatibility. Nine formulations (F1–F9) were prepared and evaluated for physicochemical properties, including weight variation, hardness, thickness, friability, and drug content, all of which complied with pharmacopoeial specifications. In vitro dissolution studies carried out in pH 1.2 acid buffer and pH 6.8 phosphate buffer showed that Xanthan gum produced a faster drug release than HPMC K100M, whereas the combination of both polymers effectively sustained drug release for 24 hours. Among all formulations, F9 exhibited the highest cumulative drug release (99.74% in 24 hours) and was selected for further evaluation. Drug release kinetics of F9 followed zero-order kinetics ($R^2 = 0.993$) with anomalous non-Fickian diffusion, indicating controlled drug release through a combination of diffusion and polymer relaxation mechanisms. Accelerated stability studies conducted for three months confirmed that the optimized formulation remained stable without significant changes in its physicochemical properties or drug release profile.

CONCLUSION

The study successfully developed controlled release matrix tablets of Azilsartan Medoxomil using HPMC K100M and Xanthan gum. Among the developed formulations, F9 was identified as the optimized formulation, providing sustained drug release for 24 hours with

99.74% cumulative drug release, acceptable physicochemical characteristics, zero-order release kinetics, and anomalous non-Fickian diffusion. Stability studies further confirmed the formulation's suitability under accelerated storage conditions. Therefore, the optimized formulation has the potential to improve the therapeutic efficacy of Azilsartan Medoxomil by maintaining prolonged drug release and reducing dosing frequency. However, further in vivo and pharmacokinetic studies are recommended to establish its clinical performance and therapeutic effectiveness.

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