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QBD DIRECTED FORMULATION AND EVALUATION OF MINI TABLETS COMBATING AZILSARTAN

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ABSTRACT

The present study aims to design and optimize the Azilsartan Mini tablets formulation using the Quality by design (QbD) approach. A randomized two factorial experimental design was used to characterize the effect of the critical factors by varying the quantity of Hypromellose, Povidone PVP K and ethyl cellulose and assessed for their impacts on the critical quality attributes (responses), including friability, dissolution time, and content uniformity. The drug-excipients interaction of the formulation was investigated using FTIR and DSC, respectively. The accelerated stability study at 40 °C/75% relative humidity and real time stability study at 25 °C/60% relative humidity was performed. FTIR revealed an absence of any significant chemical interaction in solid state. The formulations exhibited acceptable friability (0.2 to 0.9%). The dissolution study of all eleven formulations ranged from 79 to 97%. The overall study showed that the optimum level of independent factors was found to be 4mg of hypomellose, 6 mg of ethyl cellulose and 4 mg povidone PVP K in each tablet. Accelerated stability studies showed the compendial acceptable hardness and friability. The application of QbD approach can help in the detailed understanding of the effect of CMAs and CPPs on the CQAs on Azilsartan final product.

KEYWORDS: Azilsartan, Mini tablets, Quality by Design, Friability, Hypomellose.

1. INTRODUCTION

Mini tablets are tablets with diameters ≤ 3 mm and have a wide application area. For ease of use, they are usually filled in capsules, or they can be compressed in larger tablets or filled into sachets.[1,2] Mini tablets are produced with multiple punches using eccentric or rotary tablet press machines. Apart from productivity, the use of multiple punches in their production increases the amount of dust that can be consumed at a time. Thus, the fill time is shortening. In consequence of the short waiting time, the separation of the powders is prevented.[2,3]

Benefits of multiple punches

This approach helps increase productivity without the need for different production equipment, as only the mold cost is involved. It shortens the overall working time, and no separate equipment is required to collect the products obtained. Owing to all these features, the overall cost of the process remains low.[4] During tablet manufacturing, powders should be provided with mechanical resistance to facilitate the process of coating and capsule filling; this resistance can be obtained via good selection of formulation components such as binders and lubricants. Additionally, particle size plays an important role in mechanical resistance. A study carried out in 1998 by Lennartzand Mielck to improve the compactibility of paracetamol powder mixtures, they discussed the role of tablet content, size and pressure on capping tendency and tensile strength. It was found that particle size reduction has increased the mechanical resistance and decreased capping tendency, which can be explained by the elevated ratio of surface area/volume in mini tablets compared to that in conventional tablets. Therefore, increasing amount of mixture will increase the friction in punch and die wall; thus, leading to obtain a homogeneous distribution of densities.[5, 6]

Azilsartan Medoxomil (AZIL) is an Angiotensin II receptor antagonist, used to treat high blood pressure (hypertension). Chemically, it is Benzimidazole derivative (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 practically insoluble in water and freely soluble in methanol, dimethylformamide, dimethyl sulfoxide, soluble in acetic acid, slightly soluble in acetone.

Under the Quality by Deign (QbD) paradigm, new pharma product must be correctly designed to take into account the disease and its impact on the patient; the patient population; the drug properties; the preferred route of administration (from a clinical and a marketing perspective); and the requirements of the organization manufacturing the product. The preferred dosage form will usually be an oral solid dosage form (OSD), usually a tablet, which are relatively cheap to manufacture and administer, and can be produced with a wide range of release profiles. Drug substance properties must be taken into account when developing the product formulation and manufacturing process. Selection of a sub-optimal process or formula may result in considerable extra costs and delays, and even failure.

Each process has its own Critical Process Parameters (CPPs), and is affected by the Critical Quality Attributes (CQAs) of the drug substance. The Product Control Strategy (PCS) is based on understand the links between the formula and process, and the CPPs and CQAs, so generating the data to support the PCS is key to meeting the regulatory expectations of QbD.

2. MATERIAL AND METHOD

2.1 Material

Azilsartan Medoxomil was procured from Piramal Pharma Ltd. Micro crystalline cellulose (Avicel PH 102) from Dupont, Mannitol (PearlitolSD100) from Roquette and Magnesium Stearate excipients were procured from Peter Griven.

2.2 Method

2.2.1 Preparation of Mini tablets

Azilsartan Medoxomil is an angiotensin II receptor blocker indicated for the treatment of hypertension, either alone or combination with other antihypertensive agents. The excipients include Avicel PH 102 and Mannitol (Pearlitol SD 100) used as tablet filler, Hypromellose (Methocel K 4 M) used as polymer, Ethyl cellulose acts as pH independent sustained release polymer, Povidone acts as pore former whereas Colloidal Silicon Dioxide (Aerosil 200 Pharma) used as glidant.
Weighed all the components (Table 1) on an analytical balance (Shimadzu® Corporation, Kyoto, Japan). All of the powders, except the magnesium stearate, were sieved in a 1.18 mm mesh (Bronzinox, São Paulo, Brazil). They were transferred in sequence to a polyethylene bag and manually mixed for 10 min. This mixture was granulated with Isopropyl alcohol and dried for 1 hour at 44℃ product temperature. After drying, dried granules sifted through 1 mm screen. After this step, the magnesium stearate was sieved into 0.42 mm mesh (Bronzinox, São Paulo, Brazil) and added to the other components for final mixing for 2 min. Finally, the material was transferred to the tablet press machine.

The uniformly mixed batches of powder blend were compressed using multi-punch compression machine (Trover, Pharmamec, India) fitted with a tablet punch of 3 mm diameter.

Table 2.1: Formulation for preparation of Mini tablets.

Sr. No.	Ingredient	Quantity in mg										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Azilsartan Medoxomil	21.34	21.34	21.34	21.34	21.34	21.34	21.34	21.34	21.34	21.34	21.34
2	Micro crystalline cellulose (Avicel PH 102)	8.25	8.25	8.25	8.25	8.25	8.25	8.25	8.25	8.25	8.25	8.25
3	Mannitol (Pearlitol sd100)	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00
4	Hypromellose (Methocel K 4 M)	4	12	12	12	8	8	4	8	4	12	4
5	Ethyl Cellulose 7 cps	14	14	6	14	10	10	6	10	6	6	14
6	Povidone PVP K 30	4	4	12	12	8	8	4	8	12	4	12
7	Colloidal Silicon Dioxide (Aerosil 200 Pharma)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
8	Magnesium Stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50

2.3 Evaluation of developed mini tablets

All the compressed mini tablet were subjected to various parameters post compression evaluation. These include assay, uniformity of weight and content, friability and hardness testing, tablet diameter and thickness.[7- 9]

2.3.1Weight variation

Twenty mini tablets were selected randomly from each of the prepared batches to perform the uniformity of weight. These were weighed on an electronic weighing balance and the mean weight was calculated. Percentage weight variation was calculated and recorded.[10]

2.3.2 Friability

Ten pre-weighed mini tablets were selected randomly from each of the prepared batches individually and placed in the drum of the friabilator (Roche Friabilator). The friabilator was rotated at 25 rpm for 4 min. After the completion of stipulated time, the mini tablets were subjected to dusting by a microfiber cloth and the final weight of the mini tablets was measured and recorded. The percentage loss in weight was calculated and taken as a measure of friability. The experiment was carried out in triplicate and mean data was recorded.[11]

2.3.3 Hardness

The average breaking strength of mini tablets were determined by Monsanto hardness tester. Ten mini tablets were selected randomly and their strength was tested. The mean response of hardness was recorded.[12]

2.3.4 Diameter and thickness

Average diameter and thickness of the prepared mini tables were measured using Vernier Caliper. The process was performed in triplicate and the mean diameter and thickness of the mini tablets were recorded.

2.3.5 Content Assay of Mini tablets

The in-house developed and validated RP-HPLC method was employed for the evaluation of content of API in formulated mini-tablets. The Agilent Tech. (1100) equipment, was used with Fortis C18 column (100 x 4.6 mm id with 2.5 mm particle size) as stationary phase. The selected mobile phase was HPLC grade acetonitrile, and distilled water maintained at pH 5.4 using ortho phosphoric acid (OPA) in the ratio of 40:60. Detection was carried out at a 249 nm wavelength. The flow rate was maintained at 0.75 millilitre per minute. The drug's quantitative value was calculated by calculating peaks with the help of the CHEMSTATION 10.1 programme.[13]

An equivalent weight (0.100 gm) of the drug is weighed and transferred in volumetric flask containing 5ml of methanol. Dissolved the drug in methanol and make up the volume upto 100 ml with methanol. From the above prepared stock solution, pipette out 1 ml of solution and made volume upto 10 ml acetonitrile (used as diluent).

2.3.6 Dis.solution testing[15]

The USP dissolution apparatus II (paddle type) was used consists of a special, coated paddle that minimizes turbulence due to stirring. The paddle is attached vertically to a variable-speed motor that rotates at a controlled speed.

The apparatus was maintained at a rotation speed of 50 ± 4 rpm and a temperature of 37 ± 0.5 °C. Capsules filled with mini tablet containing Azilsartan medoxomil was placed in basket assembly in dissolution flask (each of the 6 dissolution vessels) containing dissolution media in ph 6.8 phosphate buffer. The study was continued in the media for next 12 h. An aliquot of 10 ml was taken from each of the dissolution vessels at 1, 3, 6, 8 and 12 hrs respectively. The withdrawn medium was replaced by using fresh medium to maintain sink condition. The withdrawn samples were filtered using syringe filter (0.45 µm). The samples were analyzed by the HPLC method mentioned above (in assay section).

Table 3.1: Evaluation of Mini Tablets.

2.3.7 Statistical Analysis of the Design of Experiments

To assess which factors would have an influence on the release of API from the coated mini-tablets, a statistical analysis of the DOE was performed using the Statistical 11.0 program (StatSoft Inc., Tulsa, OK, USA). The dissolution efficiency (DE%) was evaluated as a dependent variable, and was calculated using the Microsoft Excel add-in DD Solver.[16]

2.3.8 Pharmacokinetic study of the statistically approved formulation

Pharmacokinetic parameters such as peak plasma concentration (Cmax), time at which Cmax occurred (Tmax), area under the curve (AUC), biological half life (t1⁄2), CL/F oral clearance, CLr renal clearance, Fe fraction excreted, Tmax time to maximum concentration, T1/2 half-life, Vz/F apparent volume of Distribution were calculated in each case using the data by Kinetica™ 2000 software (Inna Phase Corporation, U.S.A) using non-compartmental approach.

2.3.9 Peak plasma concentration (Cmax)

Cmax is the maximum plasma drug concentration obtained after oral administration of drug. Cmax is the highest observable concentration obtained from the plasma concentration-time curve.

2.3.10 Time to reach peak plasma concentration (Tmax)

Tmax corresponds to the time required to reach maximum drug concentration after drug administration.

2.3.11 Area under the plasma concentration curve (AUC).

AUC0-t is the area under the plasma drug concentration versus time curve from time zero to time t is measured by the following equation.

$$AUMC_{0-t} = \int_0^t tCpdt$$

Where, Cp represents plasma drug concentration and n represents number ofsamples.

3.0 RESULT AND DISCUSSION

3.1 Evaluation of Developed Mini tablets

The tablets for sustained release were prepared and evaluated further for different parameters including weight variation, friability, hardness, diameters, thickness, disintegration test (min), assay and dissolution test.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Weight variation (%)	0.12	0.13	0.11	0.17	0.11	0.14	0.11	0.14	0.17	0.12	0.13
Friability (%)	0.31	0.31	0.32	0.33	0.29	0.31	0.19	0.29	0.23	0.25	0.21
Hardness (N)	14.2	15.1	14.9	15.1	14.8	14.9	14.7	15.1	14.9	15.2	15.3
Diameters (mm)	3.07	2.98	2.89	2.99	3.00	2.99	3.1	3.09	3.09	2.96	3.00
Thickness (mm)	2.57	2.72	2.78	2.99	2.55	2.33	2.59	2.64	2.34	2.55	2.38

The prepared mini tablets of Azilsartan Medoxomil (F1 to F11) for sustained release were found to have sufficient mechanical strength which were confirmed by their hardness (> 14 N) and the loss on friability was < 1%.

The prepared mini tablets of Azilsartan Medoxomil were observed to have uniformity in the weights, thickness and uniformity in the contents. The same mini tablets of Azilsartan Medoxomil were disintegrated within time as specified in Indian Pharmacopoeia.

3.2 *Content Assay*

The content of Azilsartan Medoxomil was analysed by using the In-house HPLC method with calibration equation of y = 23.032x - 1729.6. The percent content of Azilsartan was calculated and it was found it the range of 91-107 %.

3.3 *In-vitro* drug release

The formulations were further studied for percent drug release. The range of percent of drug release was of all formulations was 79.75-97.2 %. Formulation F7 showed better (97.2%) of drug release as compared to other formulations.

Table 3.3.1: Percentage of cumulative drug released of mini tablets.

	Run	AM1	AM2	AM3	AM4	AM5	AM6	AM7	AM8	AM9	AM10	AM11
	Time in hours	% Dissolution										
DOE 03	1	17	15	18	16	18	15	27	18	22	17	16
	3	36	43	45	35	46	44	46	47	51	43	44
	6	57	61	64	54	64	62	67	65	68	60	66
	8	71	71	77	70	75	72	81	75	79	74	79
	12	86	82	89	86	88	83	97	86	90	86	84

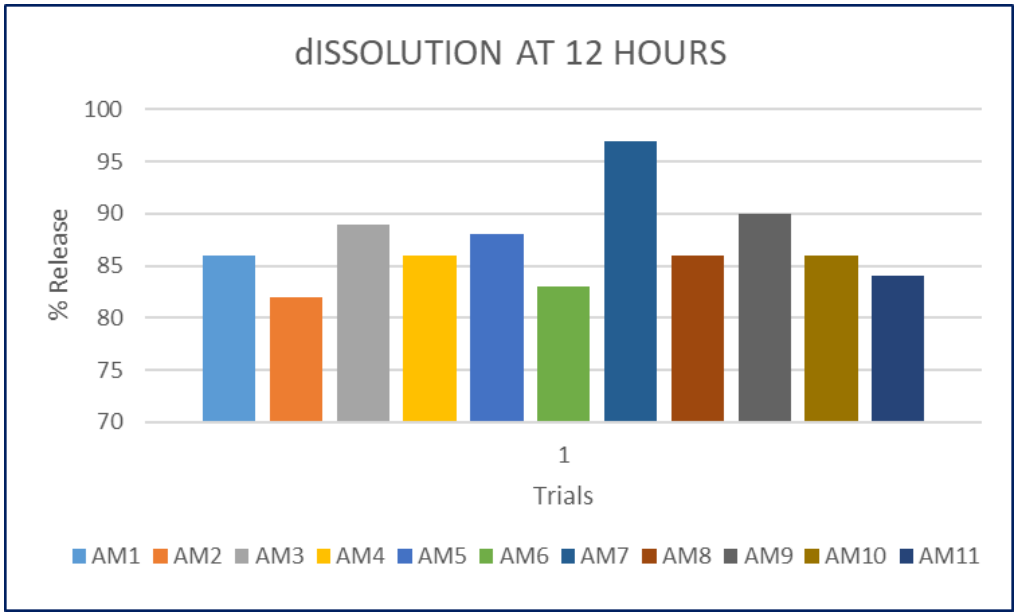


Figure3.3.1: Graphical representation of percentage cumulative drug released from selected formulations using HPLC.

3.4. Design of Experiments (DOE) for mini-tablets containing Azilsartan.

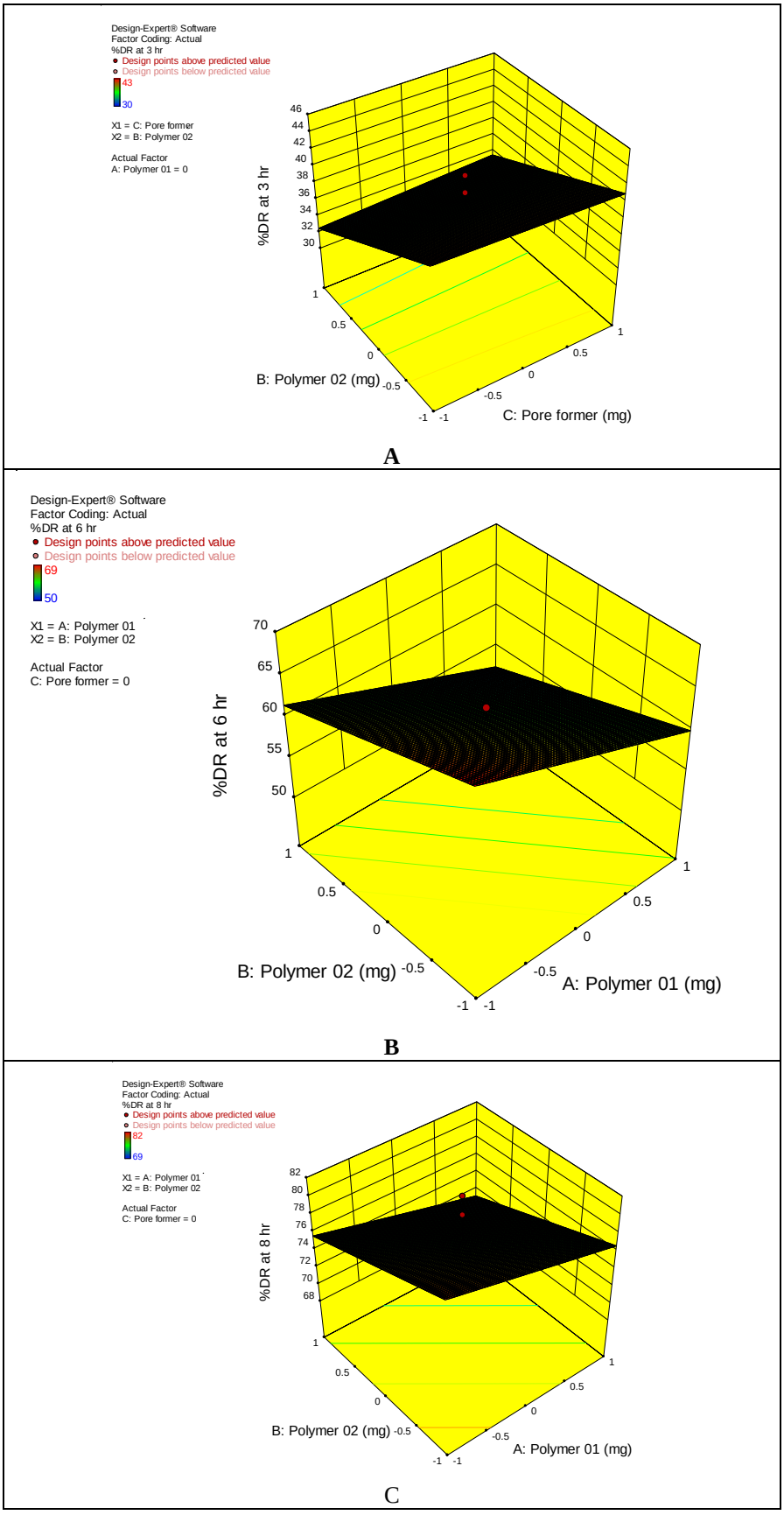


Figure 3.3.2: Response surface graph for % DE A: At 3 hrs; B: At 6 hrs; C: At 8 hrs.

In figure 2A, Contour plots is showing results in positive direction such that % drug release is almost proportionally similar to conc. of polymer 02 (Ethyl cellulose). Moreover, model is significant with p value

0.0045. In figure 2B, Contour plots is showing interaction of two polymer one is Hypromellose and other is Ethyl cellulose. Both polymers are having synergistic impact on drug release at 6 hours. Moreover, model is significant with p value 0.0210. In figure 2C, Contour plots is showing interaction of two polymer one is Hypromellose and other is Ethyl cellulose. Both polymers are having synergistic impact on drug release at 6 hours. Moreover, model is significant with p value 0.1990. From the counter plot it has been observed that pore former has not impact on controlling the drug release but polymer has impact. As discussed, earlier pore former will make channels to mobilise the drug from matrix. However, with increase in the level of Ethyl cellulose, it exhibited decrease in drug release at 06 hours.

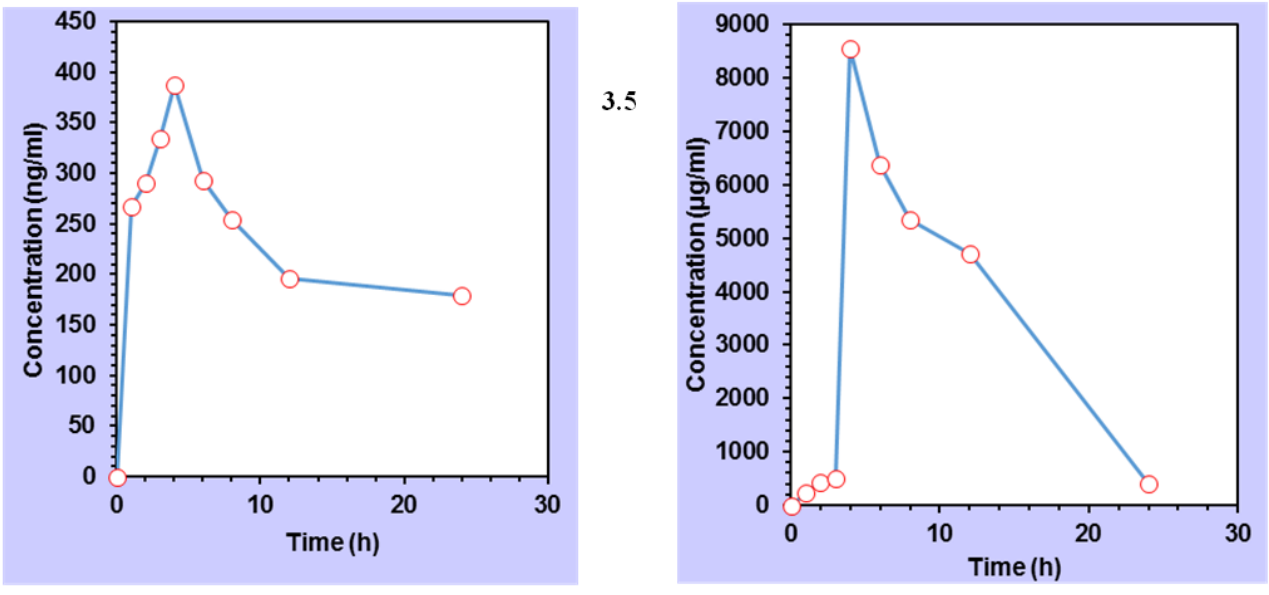
3.3 Pharmacokinetic Study of F7

The formulation F7and API with dose 4 mg/ kg were administered (Equivalent to API 1.33 mg/kg). The pharmacokinetic parameters were compared displayed in table 5.17. The concentration of drug was found to be higher in blood when the drug administered in the form of CF5 formulation. There was increase in the MRT was observed. The half-life time is 9.75 h which is significantly increased that normal API group. The Eudragit containing coated tablet has comparatively exhibited promising results compare to other formulation. however, for the immediate release F3 is a choice of formulation as the release is rapid.

Table 3.3.2: Pharmacokinetic study of formulation.

Sr. No.	Parameter	API	F7
1.	Lambda_z (1/h)	0.15	0.02
2.	AUC0–24,ngh/mL	4211 5107	4211 5107
3.	AUC0–inf,ngh/mL	4273 5254	4273 5254
4.	Cmax,ng/mL	736	705
5.	Tmax,h	3.0 2.1	3.0 2.1
6.	T1/2,h	3.90 4.43	3.90 4.43
7.	CL/F,L/h	1.17 0.952	1.17 0.952
8.	Vz/F,L	6.59 6.09	6.59 6.09
9.	CLr,L/h	0.119 0.0507	0.119 0.0507

3.4 Half Life: elimination half-life; Tmax: time to reach maximum concentration; Cmax: maximum plasma concentration; AUC: Area under curve.



API **F7**

Figure 3.3.3: Graphical representation of Pharmacokinetics study profile single API (Azilsartan) and mini tablets formulation containing Azilsartan.

Stability Study

Stability study was conducted on final formulation for 06 months at accelerated and long term stability condition i.e. 40^0C / 75% RH and 25^0C / 60% RH respectively. Trial no 07 from last DOE trial 03 was selected as an final composition for stability study. Following table capture the stability data for said batch.

Table 3.5.1: Stability Data.

Stability Condition and time points	Initial	40^0C and 75% RH			
		1 month	2 months	3 months	6 months
Appearance	Round white color biconvex tablets	Complies	Complies	Complies	Complies
Assay	100.1	100.0	99,5	100.1	99,7
Water by KF	1.6	2.1	2.2	1,9	2.2
Degradation product					
Single unknown maximum impurity	0.14	0.14	0.14	0.10	0.16
Total impurity	0.24	0.22	0.21	0.22	0.23
Dissolution: (Media: pH 6.8 Phosphate buffer, 50 rpm, 900 ml, paddle with sinker for capsules containing mini tablets)					
1	27	23	25	24	23
2	46	43	46	43	44
4	57	53	54	57	58
8	81	78	80	77	81
12	97	96	95	97	96

Table 3.5.2: Stability Data.

Stability Condition and time points	Initial	25^0C and 60% RH			
		1 month	2 months	3 months	6 months
Appearance	Round white color biconvex tablets	Complies	Complies	Complies	Complies
Assay	100.1	99.7	99.7	99/9	100.0
Water by KF	1.6	1.7	1.7	2.0	2.1
Degradation product					
Single unknown maximum impurity	0.06	0.07	0.06	0.07	0.07
Total impurity	0.15	0.14	0.14	0.14	0.16
Dissolution: (Media: pH 6.8 Phosphate buffer, 50 rpm, 900 ml, paddle with sinker for capsules containing mini tablets)					
1	27	27	24	24	25
2	46	43	43	49	49
4	57	53	59	59	57
8	81	80	77	79	80
12	97	94	94	95	96

Final composition on minitablets filled in capsules is stable for 06 months at both stability conditions. Degradation impurity growth is not observed and dissolution drop was not observed during stability study. There was no significant potency loss of Api in stability study in final encapsulated dosage form.

4.0 CONCLUSION

By varying the combination ratio of Hypromellose, ethyl cellulose and povidone PVP K, mini-tablets of Azilsartan was successfully formulated. The combination of excipients increased the dissolution rate probably due to higher capability of causing porous structure. The tablet could create good porous structure which allowed the tablet to disintegrate faster as thus improved the dissolution. Mini tablet formulated in this research work are with good acceptable pharmaceutical parameters such as uniform in size, shape, weight and drug content.

It was possible to integrate DOE to develop and optimize an extended release mini-tablet formulation containing Azilsartan. The statistical designed evaluation of the formulations led to an understanding of the main parameters that control the drug release, thereby helping in the selection and optimization of the mini tablet formulation. Final formulation is also stable for 06 months as per stability data.

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CONFLICTS OF INTEREST
Nil.

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