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FORMULATION AND EVALUATION OF EXTENDED RELEASE ALFUZOSIN HYDROCHLORIDE TABLETS

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Abstract: Preformulation studies indicated that the drug had passable flow property and good compressibility. From the drug-excipient interaction study it was observed that there was no significant physical change in the drug when mixed with excipients and kept under stressed conditions for one month. Absence of interaction between the drug and the excipients was confirmed by FTIR graph of pure drug and with various excipients.

Based on the innovator's product the target *in vitro* release profile was set to 10-20% at 1 hr, 20-30% at 2 hr, 40-55% at 6 hr, 60-80% at 12 hr, 80-90% at 18 hr, and NLT 85% at 20 hr.

The matrix tablets were formulated by wet granulation technique using hydrophilic, hydrophobic and waxy polymers in various combinations. Initial trials indicated that the combination of EC & HPMC K100M based granules were not helpful in successfully retarding the release. Further addition of HCO both intra granularly and extra granularly helped in retarding the drug release. However, a combination of all these polymers was required to obtain the target release profile.

The granules were evaluated for bulk density, tapped density, carr's index, hausner's ratio and angle of repose. The prepared tablets were evaluated for thickness, hardness, percentage friability and drug content. All the results obtained were found to be satisfactory.

The final formulation having 5.8% HCO, 2.1% EC and 34.2% HPMC K100M was found to be successful in prolonging the drug release over a period of 20 hrs. The drug release was found to be by anomalous diffusion.

The prepared tablets were found to be stable at accelerated stability conditions. The prepared matrix tablets of Alfuzosin HCl would be thus helpful in reducing the dosing frequency. The method is also adoptable for large scale production.

Index Terms **–extended release, matrix drug delivery, excipients, preformulation studies, alfuzosin HCl.**

I. INTRODUCTION

Matrix drug delivery systems:

The dictionary meaning of matrix is: a) A context or framework and b) The rock in which fossils or pebbles are embedded.[11] the same concept is applied in the pharmaceutical formulations. The active pharmaceutical ingredient is *embedded or entrapped* in a *network* formed by polymers called *matrix*.

One of the major advantages of matrix devices relative to other types of CDDS is the ease of manufacture. In general, matrix devices are prepared by mixing the drug as finely divided powder with the polymer and fabricated into a desired dosage

form. The preparation of reservoir-matrix devices is more complicated due to the need to incorporate the barrier layer onto the matrix. [12]

Matrix diffusion controlled drug delivery systems: [13-15]

Recently, a great attention has been focused on the development of sustained release or controlled release drug delivery systems. Matrix system is the most common method used in the development of controlled release formulations.

Table 1: Commonly employed polymers in matrix drug delivery systems

Hydrophilic polymers	**Hydrophobic polymers**
Acrylic acid	Glyceryl monostearate
Hydroxyethylcellulose	Glyceryl behanate
Methylcellulose	Hydrogenated vegetable oil
Polyvinyl alcohol	Paraffin
Polyacrylic acid	White wax

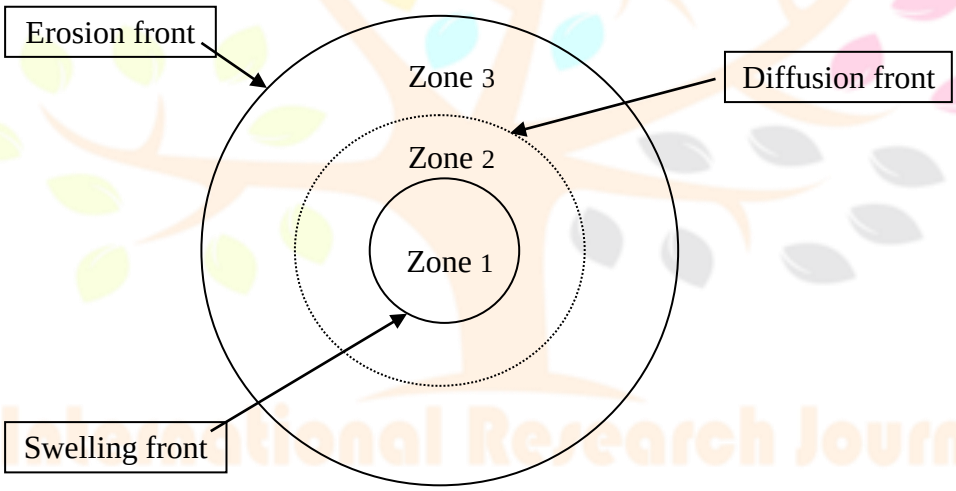


Fig 1: Matrix diffusion controlled drug delivery system.

Zone 1: Undissolved drug, glossy polymer layer.

Zone 2: Undissolved drug, gel layer.

Gel layer thickness = Difference between erosion and swelling front position.

The release of the drug from these systems is time dependent and is given by,

$$\frac{dQ}{dt} = \sqrt{\frac{AC_r D_p}{2t}} \quad \text{.....e.q.1}$$

Where, dQ/dt is the rate of drug release.

A is the loading dose.

C_r is the drug solubility in polymer.

t is the time.

D_p is the drug diffusivity in the polymer

Matrix tablets:

In these systems the drug is homogenously dispersed in the polymeric matrix, mixed along with other excipients and compressed into tablets. A variety of polymers like hydrophilic, hydrophobic, waxes, gums etc. could be incorporated alone or in combination in order to prolong the drug release.

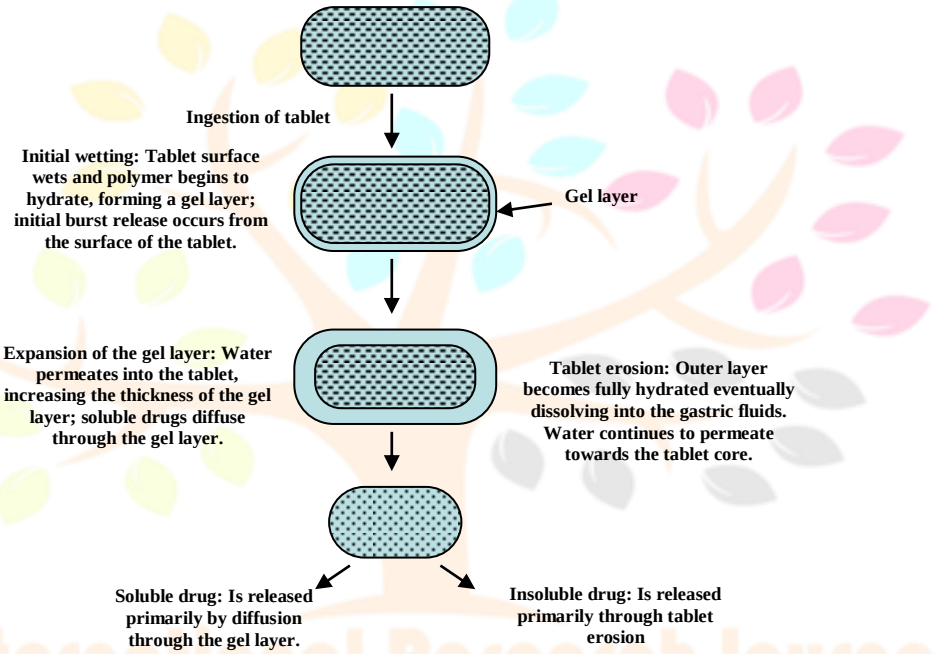
The two types of matrix systems are:

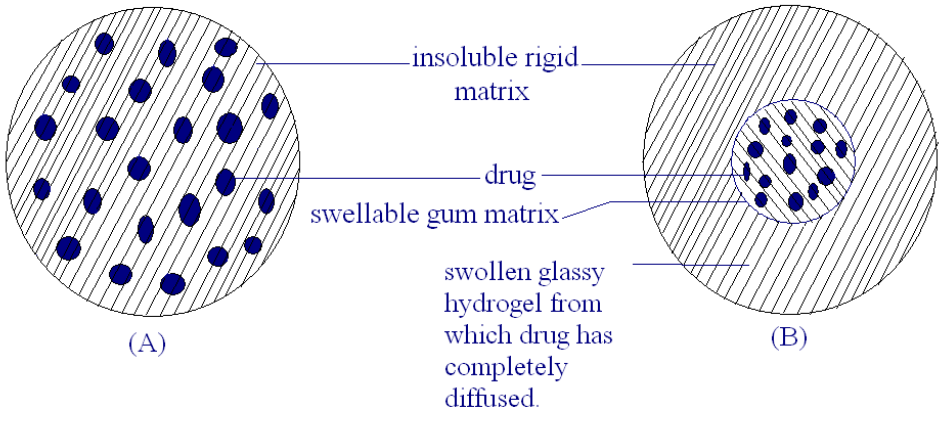
A. Matrix dissolution controlled systems.

B. Matrix diffusion controlled systems.

- Rigid matrix.
- Swellable matrix.

Fig 2: Mode of action of hydrophilic matrix dosage form





diffusion controlled devices -------- (A) rigid matrix (B) swellable matrix.

Fig 3: Schematic diagram of types of diffusion controlled device

AIM AND OBJECTIVE:

The aim of this research work was to formulate and evaluate extended release tablets of Alfuzosin HCl, to reduce dosing frequency and improve patient compliance and therapeutic action.

The specific objective of this research includes:

1. Selection of suitable polymers / polymer combinations to prepare matrix tablets of Alfuzosin HCl.
2. Evaluation of prepared matrix tablets and comparison with the innovator product.

PLAN OF WORK:

1. Preformulation studies, to check the compatibility between the drug and the excipients.
2. Design and formulation of extended release matrix tablets of Alfuzosin HCl.
3. Evaluation of precompression & postcompression parameters.
4. Stability studies.

RESEARCH METHODOLOGY:

Calibration curve of Alfuzosin HCl

UV Spectrum of Alfuzosin HCl in 0.01N HCl:

UV spectrum of Alfuzosin HCl in 0.01N HCl showed that the drug had a λ_{max} of 254nm that was exactly similar as reported.

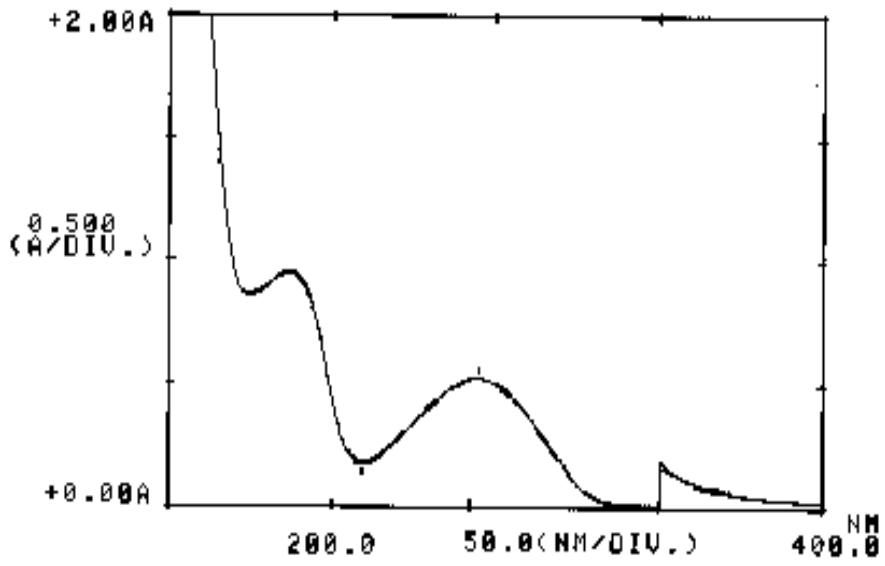


Fig 4: UV spectrum of Alfuzosin HCl in 0.01N HCl.

Calibration curve of Alfuzosin HCl:

The absorbance values corresponding to the concentration of Alfuzosin HCl solution was shown in the Table 5.1. The R squared value was found to be 0.9957 and the equation of the regression line was found to be y=0.1014x. The calibration curve of Alfuzosin HCl in 0.01N HCl is shown in Fig

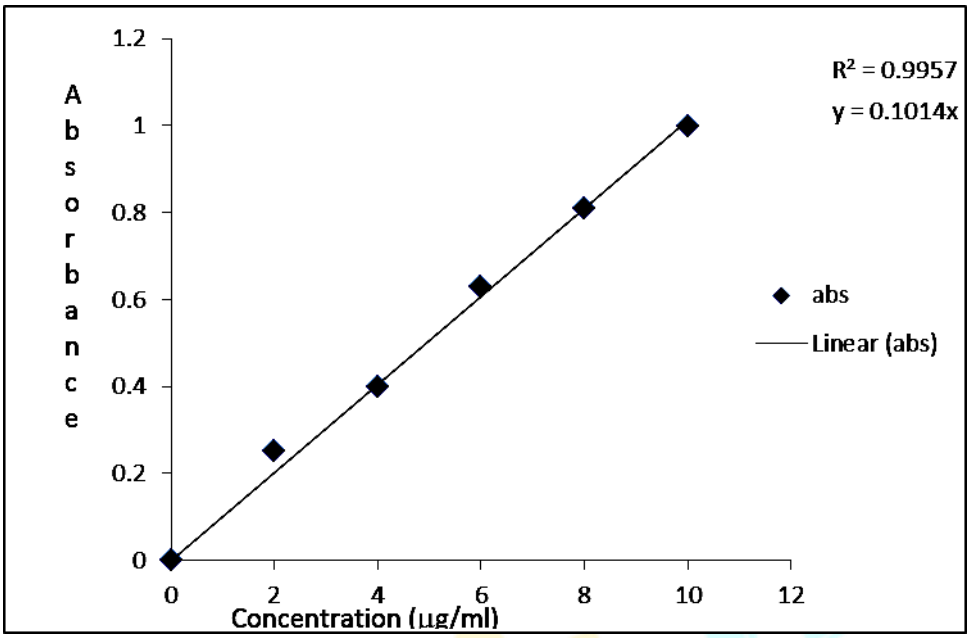


Fig5 : Standard plot of Alfuzosin HCl in 0.01N HCl.

Study on innovator product

Preformulation studies of Active ingredient

Table6 : Preformulation study of Active ingredient

Parameters	**Results**
Bulk density (gm/ml)	0.416
Tapped density (gm/ml)	0.555
Compressibility index	33
Hausner's ratio	1.39
Angle of repose	47

Drug-Excipients interaction studies:

Compatibility studies:

Table7 : Drug-Excipient compatibility studies

S.No	**Ingredients**		**Description (40°c ± 2°c, 75%±5% RH)**		
		Ratio	**Initial**	**2weeks**	**4weeks**
1.	Alfuzosin HCl		White powder	White powder	White powder
2.	Alfuzosin HCl +Lactose monohydrate	1:7	White powder	White powder	White powder
3.	Alfuzosin HCl +Ethyl cellulose 7cps	1:1	White powder	White powder	White powder
4.	Alfuzosin HCl +Isopropyl alcohol	Q.S	clear, colorless, flammable	clear, colorless, flammable	clear, colorless, flammable
5.	Alfuzosin HCl +Microcrystalline cellulose PH102	1:13	White powder	White powder	White powder

6.	Alfuzosin HCl +HPMC K100M	1:13	White powder	White powder	White powder
7.	Alfuzosin HCl +Aerosil 200	1:0.2	White powder	White powder	white powder
8.	Alfuzosin HCl +Magnesium stearate	1:0.2	White powder	White powder	White powder
9.	Alfuzosin HCl +Hydrogenated castor oil	1:2	White powder	White powder	White powder

FTIR Spectroscopy:

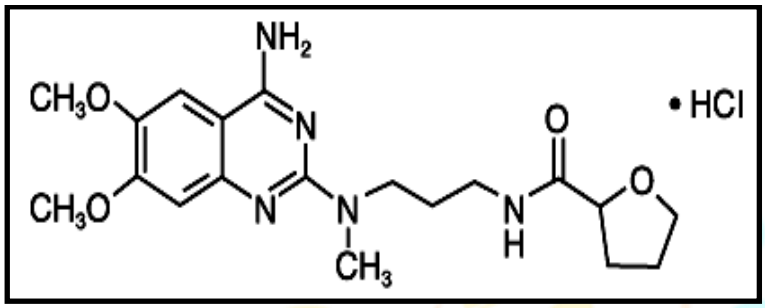


Fig6: Structure of Alfuzosin HCl

Table 8: Comparison of the characteristic IR peaks corresponding to the functional groups in Alfuzosin HCl with that of the physical mixtures.

Corresponding functional groups	Literature value(wave number cm^{-1})	Characteristic peaks of drug alone(wave number cm^{-1})	Characteristic peaks of Drug +polymer mixture (wave number cm^{-1})
Primary & Secondary amine group N-H stretching	3500-3100	3389.64	3381.21
Amide C=O stretching	1700-1650	1654.92	1653.00
Cyclic C-O stretching	1350-1250	1269.16	1261.45
Aliphatic C-H stretching	2960-2850	2933.73	2918.30

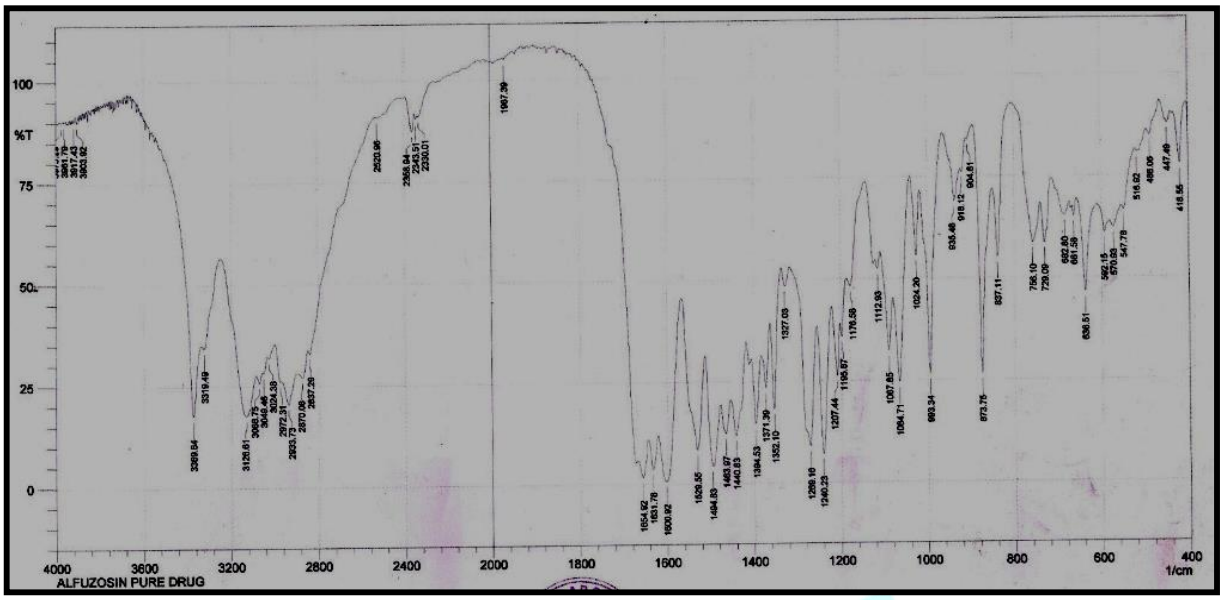
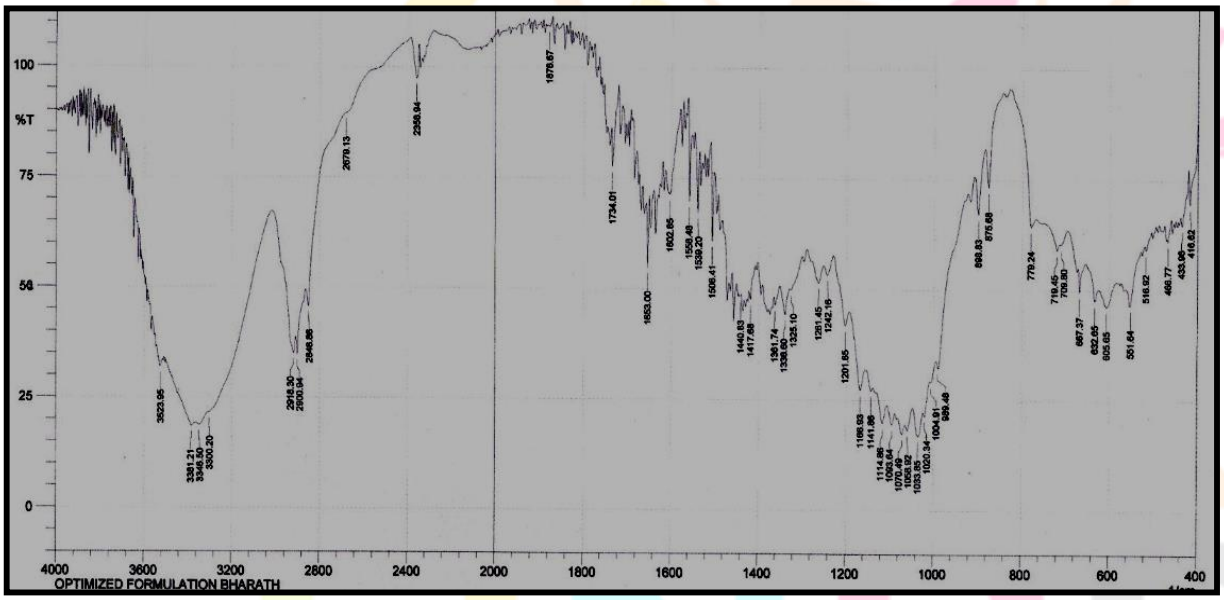


Fig 7: The FTIR spectra of Alfuzosin pure drug

Fig 8 : The FTIR spectra of the drug mixed with polymers.



Dose calculation for extended release tablets of Alfuzosin HCl

Calculation of theoretical release profile of Alfuzosin HCl:

Amount of drug needed to be extended = $\frac{0.693 \; x \; D \; x \; T}{t_{1/2}}$ **……e.q 13**

Where,
D = dose of the drug (2.5mg).
T = duration of time desired for extended release (24h).
$t_{1/2}$ = half-life of the drug (4.5h).
Therefore, 9.24mg of the drug should be extended in each formulation.

Evaluation of extended release matrix tablets

Pre compression parameters:

The pre compression properties of the prepared granules of F4 to F10 Table

Table 9: Pre compression properties of formulations F4 – F10

Formulation	Poured density* (gm/ml)	Tapped density* (gm/ml)	Carr's index (%)	Hausner's ratio (%)	Angle of repose* (degrees)
F4	0.51 ± 0.006	0.39 ± 0.004	12.82	1.15	23 ± 1.537
F5	0.45 ± 0.007	0.52 ± 0.008	13.46	1.16	25 ± 2.654
F6	0.48 ± 0.013	0.41 ± 0.035	14.63	1.17	26 ± 0.546
F7	0.36 ± 0.02	0.42 ± 0.007	14.28	1.17	24 ± 2.961
F8	0.398 ± 0.006	0.448 ± 0.023	11.16	1.13	23 ± 1.852
F9	0.381 ± 0.016	0.459 ± 0.017	16.99	1.20	25 ± 2.522
F10	0.424 ± 0.004	0.556 ± 0.005	23.74	1.31	23 ± 2.196

*The values represent mean ± SD, n = 3.

Post compression parameters:

The properties of tablets like thickness, hardness and friability, average weights, drug content for the formulations F4 – F10 are shown in Table 5.9. The values of drug content uniformity and weight variation are shown in Table 5.10.

Table 10: Postcompressional evaluation of formulations F4 – F10

Formulation	Thickness[A] (mm)	Hardness[B] (Kg/cm^2)	Friability (%)	Avg. weight (mg)	Drug content (mg)
F4	4.2 ± 0.089	8.0 ± 0.540	0.094	380±2	99.3±1.4
F5	4.2 ± 0.518	6.0 ± 0.550	0.223	380±2	98.7±1.4
F6	4.2 ± 0.290	9.0 ± 0.789	0.197	380±2	101.6±1.3
F7	4.2 ± 0.127	7.0 ± 0.681	0.064	380±2	101.2±0.9
F8	4.2 ± 0.120	8.0 ± 0.337	0.061	380±3	101.6±1.2
F9	4.2 ± 0.078	9.0 ± 0.896	0.063	380±3	99.3±1.4
F10	4.2 ± 0.041	9.0 ± 0.725	0.011	380±3	98.7±1.4

A = Average of 6 readings ± SD. B = Average of 10 readings ± SD.

Table11: Drug content uniformity and weight variation for formulations F4 – F10

Drug content uniformity* (mg)	Weight variation (%)
9.85 ± 0.14	PASS
9.45 ± 0.544472	PASS
9.97 ± 0.091924	PASS
9.25 ± 0.035355	PASS
9.72 ± 0.162635	PASS
9.94 ± 0.028284	PASS
9.86 ± 0.127279	PASS

*The values represent mean ± SD, n = 10.

***In vitro* drug release profiles:**

The *in vitro* dissolution data of formulations F1 to F10 and innovator is given in Table 5.11, the release profile of formulations F4, F5, F6, F7, F9 & F10 is shown in Fig. 5.6 and F8, innovator is shown in Fig. 5.7.

Table 12: *In-vitro* dissolution data of formulations F1 to F10 and innovator product

Formulations	% drug release						
	0hr	1hr	2hr	6hr	12hr	18hr	20hr
F1	0 ± 0	48.21 ± 1.93828	56.54 ± 2.39846	82.37 ± 0.37292	98.48 ± 2.49361	105.38 ± 3.83910	-
F2	0 ± 0	42.37 ± 2.38462	50.38 ± 2.38193	62.37 ± 1.28394	85.26 ± 2.38457	99.37 ± 2.38716	-
F3	0 ± 0	35.28 ± 2.39871	45.28 ± 2.39738	59.28 ± 2.38109	82.37 ± 1.29374	95.28 ± 1.28367	-
F4	0 ± 0	4.98 ± 0.65054	11.1 ± 4.6502	19.25 ± 2.33456	36.95 ± 2.12132	55.62 ± 1.04628	61.34 ± 3.1537
F5	0 ± 0	6.16 ± 0.51619	13.06 ± 2.59508	21.29 ± 1.28362	40.18 ± 4.7164	59.45 ± 0.27354	65.86 ± 2.54558
F6	0 ± 0	8.56 ± 0.23335	14.55 ± 0.7566	29.58 ± 2.94716	64.91 ± 1.79605	71.73 ± 2.48140	77.74 ± 2.63751
F7	0 ± 0	13.59 ± 1.8809	19.07 ± 5.14067	32.67 ± 3.48104	68.85 ± 2.87793	75.28 ± 2.03849	81.48 ± 3.67696
F8	0 ± 0	14.52 ± 1.1738	22.71 ± 0.51619	40.28 ± 0.28374	72.45 ± 0.42426	88.26 ± 0.29384	96.38 ± 0.51619

F9	0 ± 0	16.49 ± 0.52326	24.4 ± 0.70711	42.49 ± 1.2937	74.71 ± 1.03945	91.13 ± 1.55564	-
F10	0 ± 0	18.39 ± 0.33234	25.06 ± 0	41.41 ± 1.28394	72.25 ± 1.13137	92.51 ± 0.23335	-
Innovator	0 ± 0	15.33 ± 0.42236	25.42 ± 0.13983	40.25 ± 0.49284	75.11 ± 1.03467	88.29 ± 1.38294	95.06 ± 0.67897

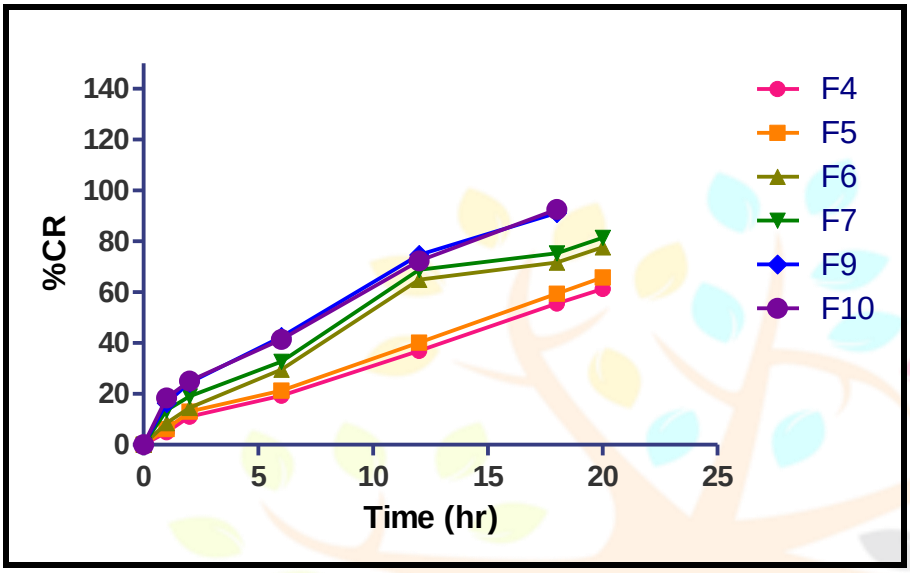


Fig9 : ***In vitro*** **drug release profile of formulations F4, F5, F6, F7, F9 & F10.**

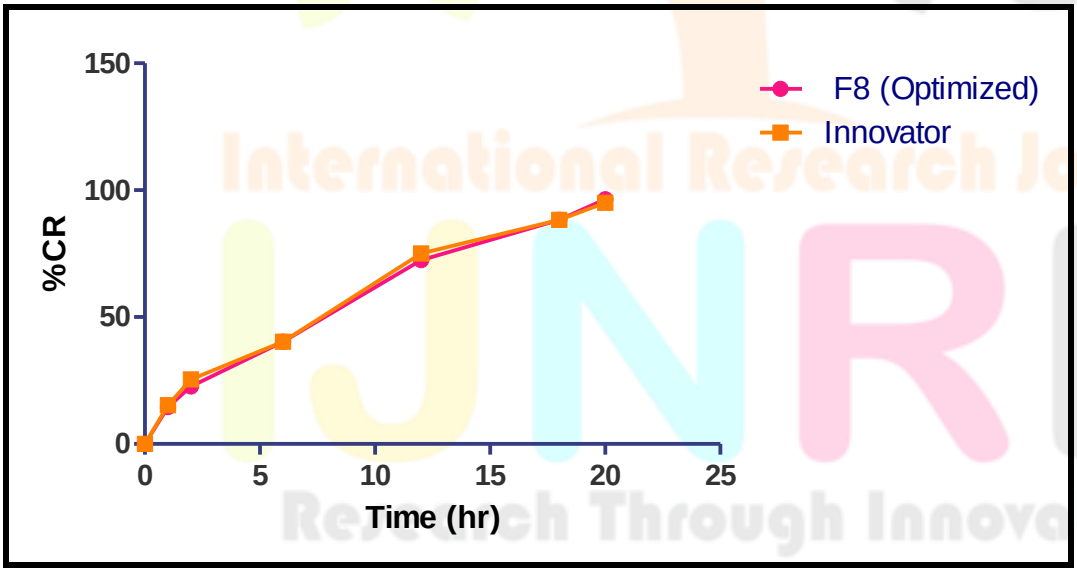


Fig10 : ***In vitro*** **drug release profile of formulations F8 (Optimized) & innovator product.**

Data treatment of *in vitro* drug release profile of F8 (optimized) and innovator with different models:

The kinetic treatment was applied to the drug release from the final formulation and innovator. The results are reported as follows:

Table 13: Regression coefficient and slope values of innovator product for various kinetic models

	Zero order	First order	Higuchi	Korsmeyer-peppas
r^2	0.9642	0.9570	0.9858	0.9898
Slope	4.465	-0.0599	21.90	0.6024

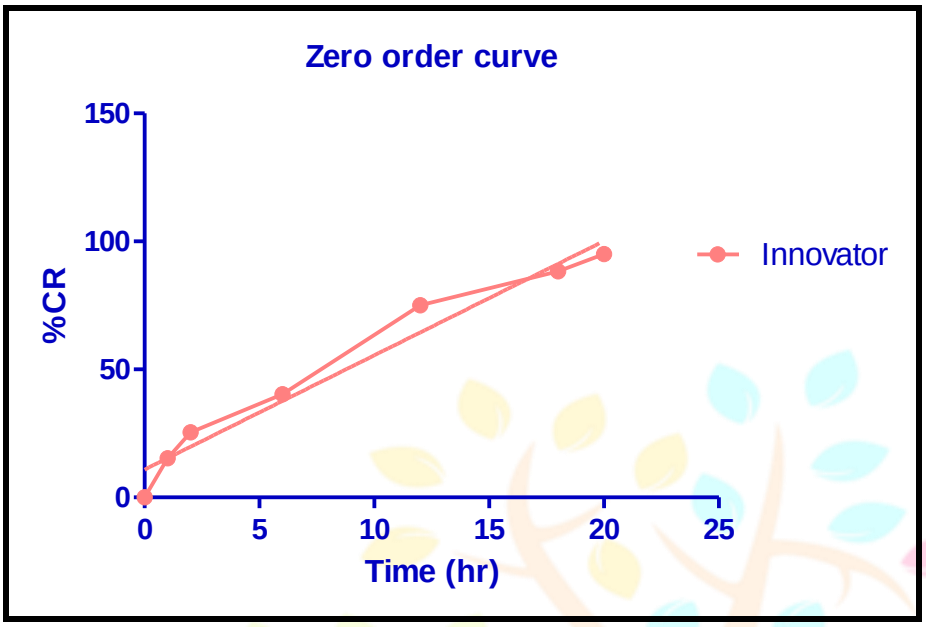


Fig 11: Zero order curve of innovator product

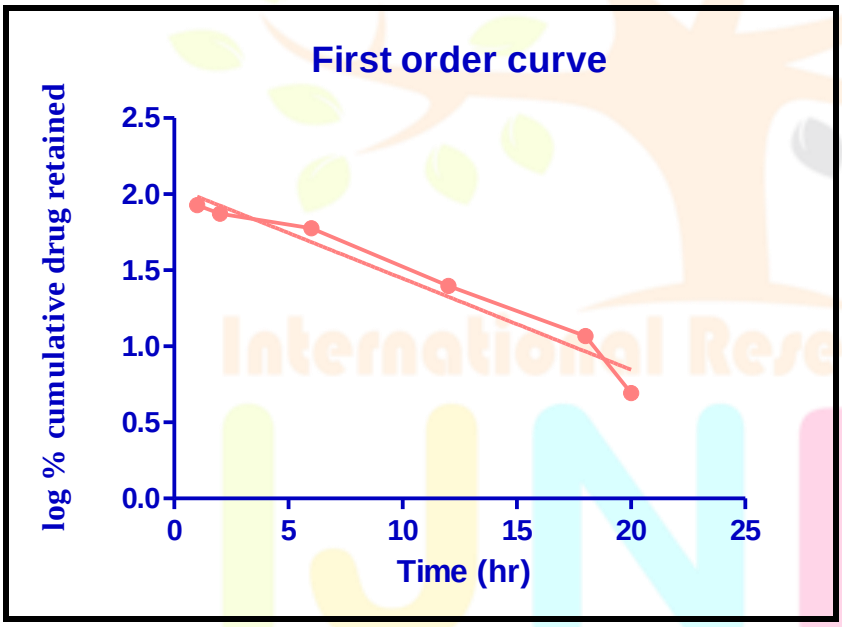


Fig 12: First order curve of innovator product

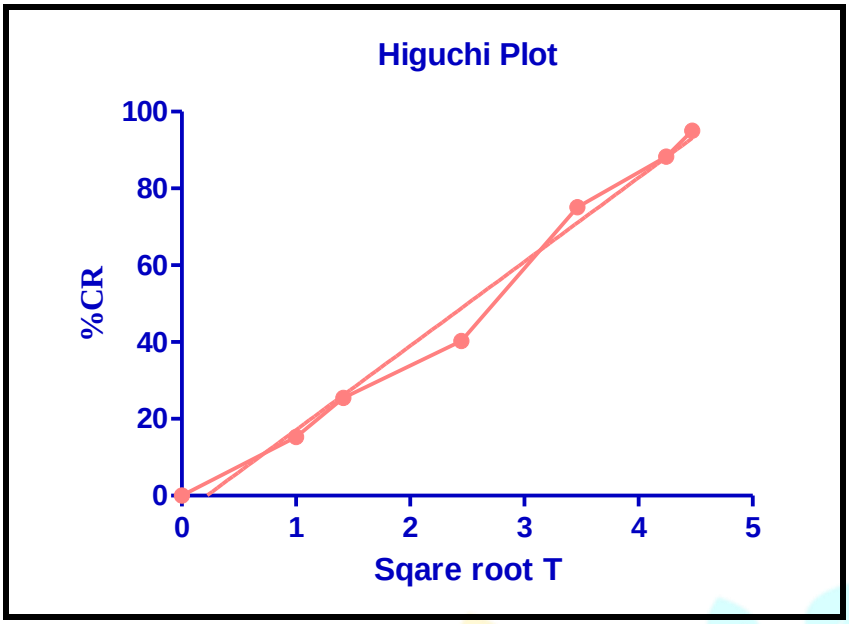


Fig 13: Higuchi plot of innovator product

Fig 14: Korsmeyer plot of innovator product

Table 14: Regression coefficient and slope values of optimized formula for various kinetic models

	Zero order	First order	Higuchi	Korsmeyer-peppas
r^2	0.9751	0.9238	0.9858	0.9956
Slope	4.535	-0.06425	22.11	0.6310


Zero hour


1st hour


6th hour


12th hour


18th hour


20th hour

Fig19: Swelling and erosion of the optimized formulation

Stability study data of the Alfuzosin HCl tablets:

Stability studies were conducted at 40°C, 75% RH for about 3 months in stability chamber and results are shown in Table 5.14 to Table 5.15.

Table 15: Stability study data of Alfuzosin HCl tablets

Parameters	Specifications	Testing intervals			
		Initial	1st month	2nd month	3rd month
Description	Off white, round shaped, biconvex tablets	Compiles	compiles	compiles	Complies
Water content	NMT 0.5% w/w	0.28%	0.33%	0.338%	0.35%
Assay	NLT 99.0% & NMT 101.0 %	99.9%	99.9%	100.6%	100.6%
Hardness	NLT 3kg/cm^2	8±0.5	9±0.5	8±0.5	9±0.5
Thickness	4.2mm	4.2±0.1	4.2±0.1	4.2±0.1	4.2±0.1

Table16: *In vitro* drug release data of optimized formulation during stability studies and comparison with innovator product

Time (hr)	% Drug release 40^{0}C / 75% RH			
	Innovator	1 month	2 month	3 month
1	15.33	14.00	14.42	14.25
2	25.42	23.45	24.34	25.26
6	40.25	43.84	42.35	43.43
12	75.11	74.23	75.34	75.29
18	88.29	85.48	86.38	85.69
20	95.06	96.26	96.38	96.38

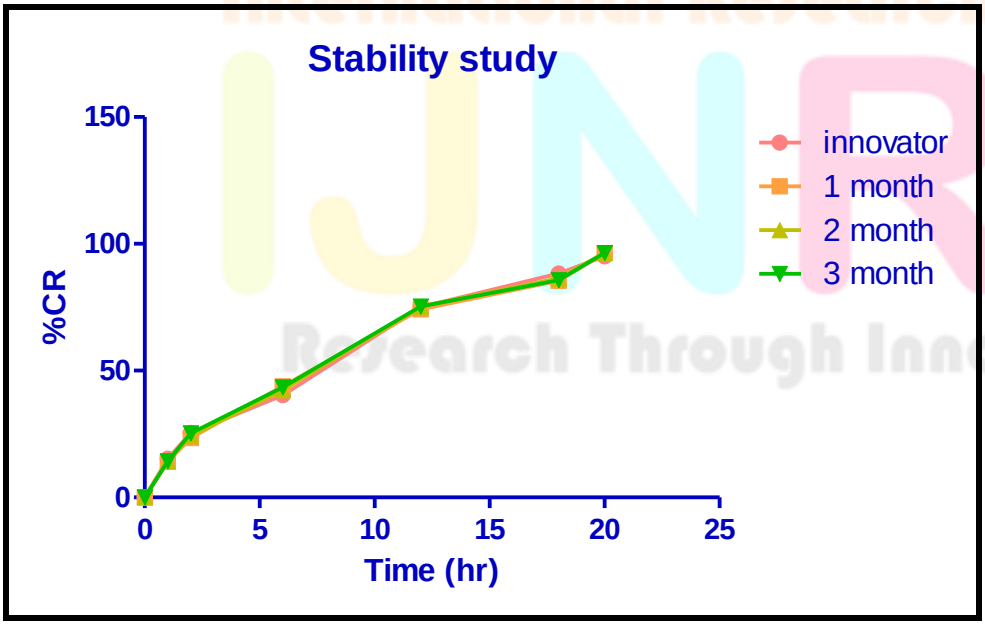


Fig 20: *In vitro* drug release profile of optimized formulation during stability studies and comparison with innovator product

II. ACKNOWLEDGMENT

To write a thesis of this magnitude, it needs a lot of patience, skill and expertise over the subject, which I have gained because of the opportunity given to me by my esteemed guide, **Dr. Uma A. Patil, Associate Professor, Department of Pharmaceutical Technology, KLE University's College of Pharmacy, Bangalore.** The facilities provided by her, enabled me to complete this work successfully and her constant guidance, supervision and encouragement paved the way for the successful completion of this research work.

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