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Formulation and *In-vitro* Evaluuation of Sustained Release Tablets of Alfuzocin by Using Natural Polymers

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A B S T R A C T

The aim of the present study was to develop sustained release formulation of Alfuzocin to maintain constant therapeutic levels of the drug for over 12 hrs. Various natural polymers such as Guar gum Sodium CMC and Chitosan were employed as polymers. Alfuzocin dose was fixed as 10 mg. Total weight of the tablet was considered as 150 mg. Polymers were used in the concentration of 25, 50 and 100 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Alfuzocin, Guar gum, Chitosan, Sodium CMC and sustained release tablets.

A R T I C L E I N F O

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1. Introduction

Alfuzosin is a pharmaceutical drug of the alpha-1 blocker class. As an antagonist of the alpha-1 adrenergic receptor, it works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate. It

is thus used to treat benign prostatic hyperplasia. Alfuzosin belongs to a class of drugs called alpha-blockers. It is used for increasing the flow of urine that is reduced by benign prostatic hypertrophy (BPH). Alpha blockers relax the muscles in the prostate gland and the neck of the bladder. This allows the urethra (the tube that conducts urine out of the bladder) to open wider so that urine flows more easily.

Extended Release Drug Therapy

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and injectables. Even today these conventional dosage forms are the primary pharmaceutical vehicles commonly seen in the prescription and over the counter drug market. The oral conventional types of drug delivery systems are known to provide a prompt release of the drug. Therefore to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue [1].

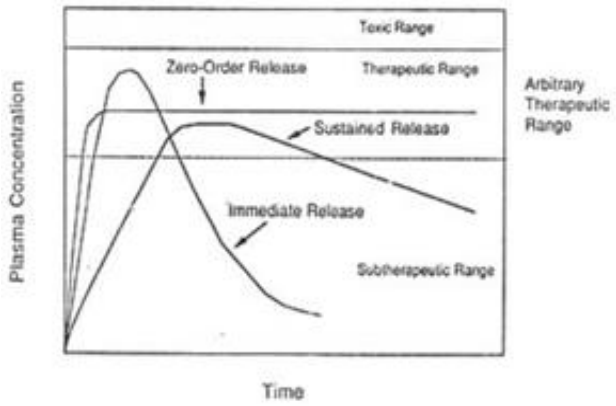

Figure 1: Plasma Level versus Time Profile Showing Different Conventional Dosage Form.

The term controlled\extended release implies a system that provides continuous delivery of the drug for a predetermined period with predictable and reproducible kinetics and a known mechanism of release. This means that the release of drug ingredient(s) from a controlled release drug delivery system proceeds at a rate that is not only predictable kinetically but also reproducible from one unit to another. In other words, the system attempts to control drug concentration in the target tissue. Extended release denotes that the system is able to provide some actual therapeutic control whether be it of temporal or spatial nature or both. In other words, the system attempts to provide a constant drug concentration in the target tissue. It is this nature of this system that makes it different from sustained release systems.

Advantages of extended release dosage form:

- Improved patient compliance and convenience due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore, better control of disease condition and reduction intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients.
- Sustained blood levels; the size and frequency of dosing are determined by the pharmacokinetic and pharmacodynamic property of drug. The use of extended releaseproducts may maintain therapeutic concentration over prolonged period.
- Attenuation of adverse effect, the use of extended release products avoids the high initial blood concentration, which may cause many side effects like nausea, local irritation, haemodynamic changes etc.

Disadvantages of extended release dosage form:

- Toxicity due to dose dumping.
- Increased cost.
- Unpredictable and often poor *in vitro- in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Local irritation or damage of epithelial lining (lodging of dosage forms).
- Need for additional patient education and counseling.
- Increased potential for first- pass clearance.

Ideal candidate for extended/controlled release drug delivery systems:

The desired biopharmaceutical characteristics of drugs to be used in the development of per oral CR dosage forms are:

Molecular weight : <1000 mg
Solubility : 0.1 mcg/ml
P^{ka} : >0.1% to 1% at pH 1 to 7.8
Apparent partition coefficient : 0.5 to 2.0
General absorbability : From all GI segments
Stability : Stable in GI environment Release should not be influenced by pH and enzymes.

Less protein binding

To evaluate whether a drug is viable candidate or not for the design of per oral CR formulation, one must consider the following pharmacokinetic parameters of the drug.

Elimination half-life : Preferably between 0.5& 8 hours
Total body clearance : Should not be dose dependent
Elimination – rate constant : Required for the design
Absolute bioavailability : Should be 75% or more
Absorption rate: Must be greater than release rate

2. Materials and Methods

Alfuzocin (hetero laboratories), Gum karaya (SD Fine Chemicals, Hyderabad), Xanthan gum(SD Fine Chemicals, Hyderabad), Guar gum (SD Fine Chemicals, Hyderabad), Mg. stearate (SD Fine Chemicals, Hyderabad), talc(SD Fine Chemicals, Hyderabad).

Determination of UV Absorption maxima:

Alfuzosin solution was prepared in 0.1 N HCL and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 298 nm. The procedure was repeated with pH 6.8 phosphate buffer.

Preparation of Standard Calibration curve of Alfuzosin:

100 mg of Alfuzosin was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1N HCl (pH 1.2) in 100ml to get 100µg/ml (working standard). Then 0.2,0.4,0.6.0.8,and 1 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 2µg,4µg, 6µg, 8µg, and 10µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 298 nm against 0.1 N HCl (pH 1.2) as blank. The absorbance so obtained was tabulated as in Table 7.1. Calibration curve was constructed and shown in Fig. 7.1.The procedure was repeated with pH 6.8 phosphate buffer and absorbance's were measured at 299 nm. The absorbances and standard graph were mentioned in Table 7.2 and figure 7.2 respectively.

Tablet formulation:

Formulation of Alfuzosin Extended release Tablet by Direct- Compression:

Composition of preliminary trials for Alfuzosin Extended release Tablet by direct compression is shown in table. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 12mm flat punch, B tooling. Each tablet contains 100mg of Alfuzocin and other pharmaceutical ingredients.

Evaluation parameters:

Precompression parameters:

1. Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below.

2. Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times & tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus).

3. Angle of Repose (Ɵ):

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

Post compression parameters:

1. Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P.

2. Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

3. Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

4. Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.

5. *In-Vitro* drug release:

In-vitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 6 hours. The samples were withdrawn at regular time intervals of 30 min, 1 hour, 2 hr, 3, 5, 6,7 & 8 hours respectively.

6. Assay: 10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in pH 1.2 buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH 1.2.

3. Results and Discussion

Standard Calibration curve of alfuzosin:

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

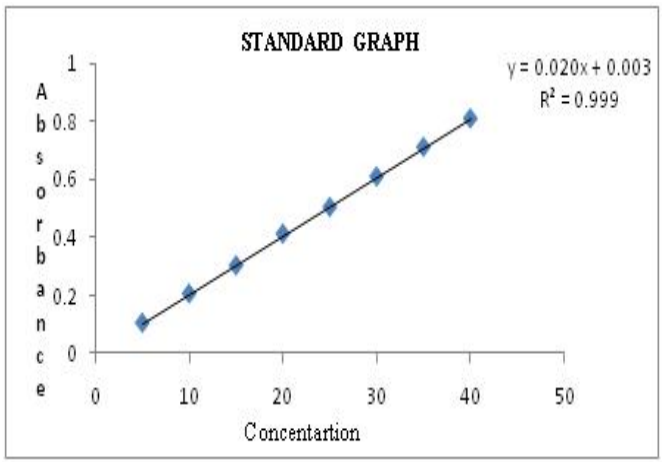

Figure 2: Standard graph of Alfuzosin in 0.1 N HCl

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

***In-Vitro* Drug Release Studies**

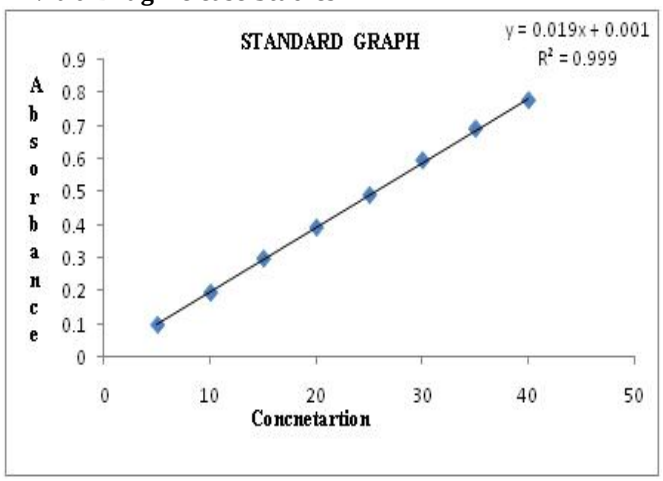

Figure 3: Standard graph of Alfuzocin p H 6.8 Phosphate buffer (294nm)

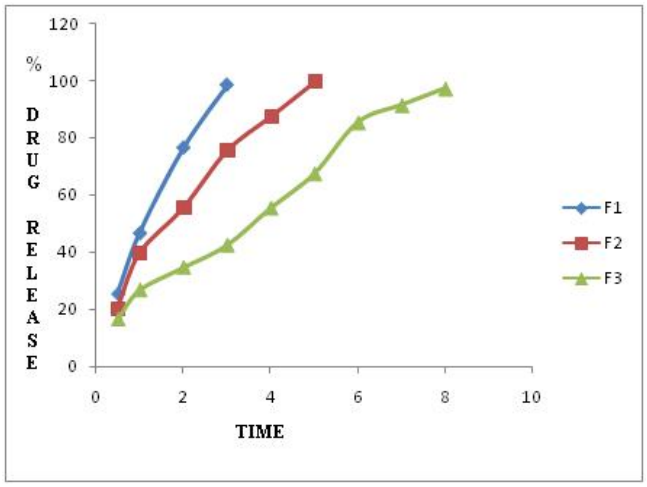

Figure 4: Dissolution profile of Alfuzocin (F1, F2, F3 formulations).

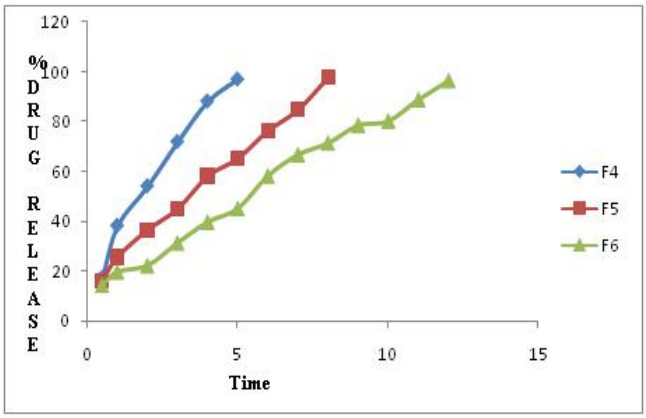

Figure 5: Dissolution profile of Alfuzocin (F4, F5, F6 formulations)

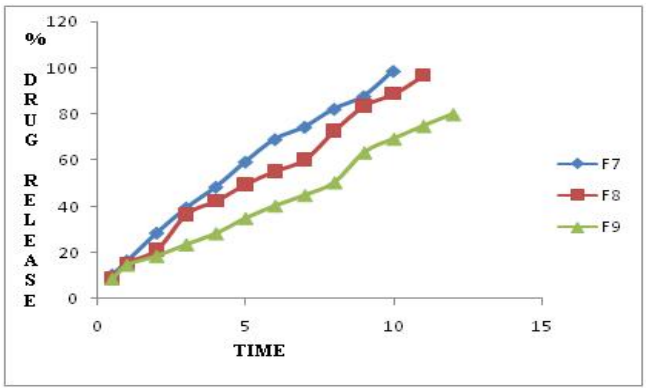

Figure 6: Dissolution profile of Alfuzocin (F7, F8, F9 formulations)

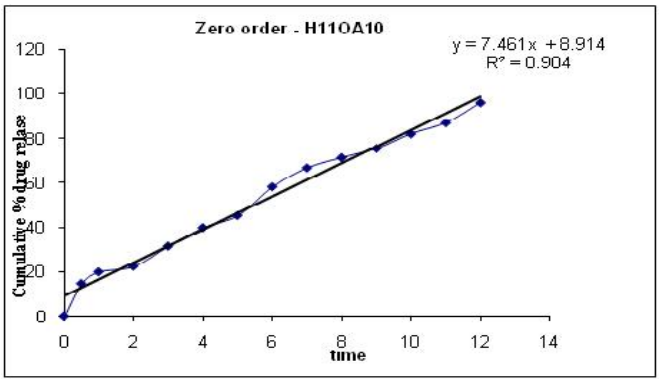

Figure 7: Zero order release kinetics graph

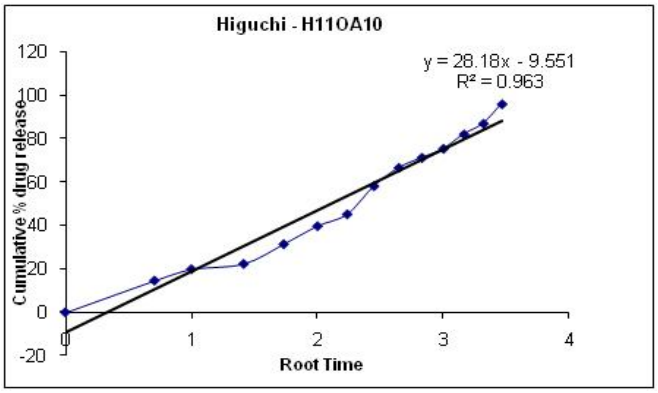

Figure 8: Higuchi release kinetics graph

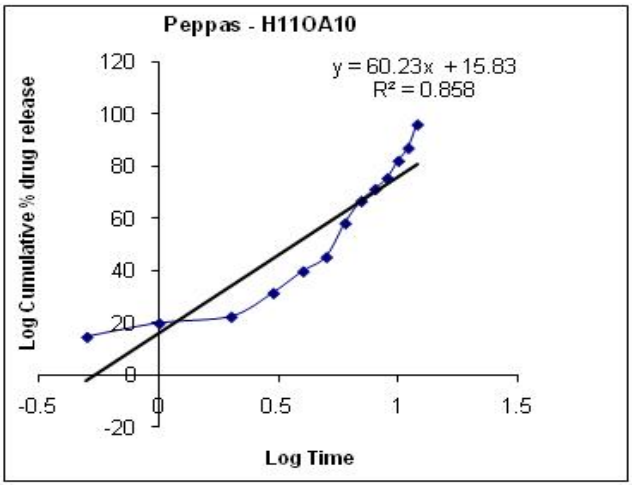

Figure 9: Kars Mayer peppas graph

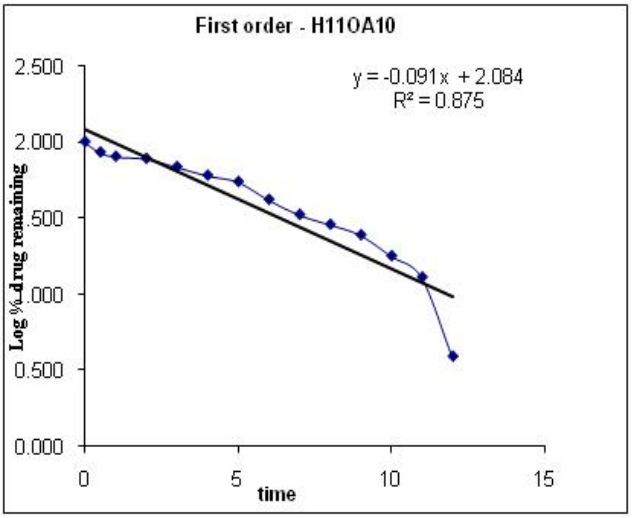

Figure 10: First order release kinetics graph

From the dissolution data it was evident that the formulations prepared with Sodium CMC as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with Guar gum retarded the drug release in the concentration of 100 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation. The formulations prepared with Chitosan showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model. From the above graphs it was evident that the formulation F6 was followed Zero order release kinetics.

4. Conclusion

The aim of the present study was to develop sustained release formulation of Alfuzocin to maintain constant therapeutic levels of the drug for over 12 hrs. Various natural polymers such as Guar gum Sodium CMC and Chitosan were employed as polymers. Alfuzocin dose was fixed as 10 mg. Total weight of the tablet was considered as 150 mg. Polymers were used in the concentration of 25, 50 and 100 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours. It followed zero order release kinetics mechanism.

Table 1: Formulation of alfuzosin Extended release tablets

Formulation No.	Alfuzocin	Sodium CMC	Guar Gum	Chitosan	Mag. Stearate	Talc	MCC pH 102
F1	10	25			4	4	QS
F2	10	50			4	4	QS
F3	10	100			4	4	QS
F4	10		25		4	4	QS
F5	10		50		4	4	QS
F6	10		100		4	4	QS
F7	10			25	4	4	QS
F8	10			50	4	4	QS
F9	10			100	4	4	QS

All ingredients are expressed in mg only

Table 2: Concentration and absorbance obtained for calibration curve of Alfuzosin in 0.1 N hydrochloric acid buffer (pH 1.2)

Conc [µg/l]	Abs
4	0.104
8	0.205
12	0.302
16	0.411
20	0.503
24	0.608

28	0.710
32	0.808

Table 3: Observations for graph of Alfuzocin in p H 6.8 phosphate buffer (294nm)

Conc [µg/l]	Abs
4	0.098
8	0.195
12	0.298
16	0.392
20	0.490
24	0.595
28	0.690
32	0.776

Table 4: Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Table 5: Post Compression Prameters

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	152.5	4.5	0.50	6.8	99.76
F2	145.4	4.5	0.51	6.9	99.45
F3	148.6	4.4	0.51	4.9	99.34
F4	150.6	4.5	0.55	6.9	99.87
F5	149.4	4.4	0.56	6.7	99.14
F6	150.7	4.5	0.45	6.5	98.56
F7	152.3	4.1	0.51	6.4	98.42
F8	151.2	4.3	0.49	6.7	99.65
F9	148.3	4.5	0.55	6.6	99.12

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 6: Dissolution Data of Alfuzocin Tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	25.5	20.1	16.4	17.25	16.42	14.62	10.4	9.4	8.5
1	46.7	39.4	26.7	38.26	25.73	19.86	16.5	15.6	14.5
2	76.5	55.3	34.6	54.16	36.63	22.35	28.6	21.4	18.4
3	98.4	75.3	42.4	72.01	45.04	31.45	39.5	36.7	23.4
4		87.3	55.4	88.26	58.25	39.80	48.5	42.4	28.2
5		99.4	67.4	97.10	65.33	45.25	59.4	49.6	34.8
6			85.4		76.41	58.24	69.2	55.3	40.2
7			91.5		84.84	66.73	74.5	60.3	44.8
8			97.3		97.80	71.34	82.3	72.8	50.4
9						75.52	87.78	83.52	63.34
10						82.17	98.78	88.65	69.27
11						87.10		96.56	74.86
12						96.10			79.97

Table 7: Release kinetics data for optimised formulation

Cumulative (%) Release Q	Time (T)	LOG (%) Release	LOG (%) Remain	Release Rate (Cumulative % Release / t)	1/CUM% Release	Peppas log Q/100	% Drug Remaining
0	0		2.000				100
14.62	0.5	1.165	1.931	29.240	0.0684	-0.835	85.38
19.86	1	1.298	1.904	19.860	0.0504	-0.702	80.14
22.35	2	1.349	1.890	11.175	0.0447	-0.651	77.65
31.45	3	1.498	1.836	10.483	0.0318	-0.502	68.55
39.8	4	1.600	1.780	9.950	0.0251	-0.400	60.2
45.25	5	1.656	1.738	9.050	0.0221	-0.344	54.75
58.24	6	1.765	1.621	9.707	0.0172	-0.235	41.76
66.73	7	1.824	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	1.457	8.918	0.0140	-0.147	28.66
75.52	9	1.878	1.389	8.391	0.0132	-0.122	24.48
82.17	10	1.915	1.251	8.217	0.0122	-0.085	17.83
87.1	11	1.940	1.111	7.918	0.0115	-0.060	12.9
96.1	12	1.983	0.591	8.008	0.0104	-0.017	3.9

5. Acknowledgement

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