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Design and Development of Alfuzosin Hydrochloride Controlled Release Tablets

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Abstract

The primary study is to develop controlled release drug delivery is to ensure safely and to improve efficacy of drug as well as patient compliance. If the drug is given in conventional dosage form, it has to be administered several times a day to produce the desired therapeutic effect, which results in frequent dosing fluctuation in plasma drug level. Drug concentration can be controlled within a narrow therapeutic range by the use of sustained release system, which also minimizes the severity of side effects. In controlled drug delivery system, oral route is the most convenient and common mode of administration, which is designed to release the drug over a controlled period of time. Oral controlled release multiple unit dosage forms (e.g.pellets, granules or microparticles) are becoming more popular when compared to single unit dosage forms. Because of the several advantages they offer. The present study is to develop a stable and robust manufacturing process for alfuzusin HCL controlled release tablets when scaled up from lab scale to pilot scale. When various physical parameter of the product were confirmed.

Keywords: Controlled release drug delivery, alfuzusin HCL, pilot scale, single unit dosage

I. INTRODUCTION

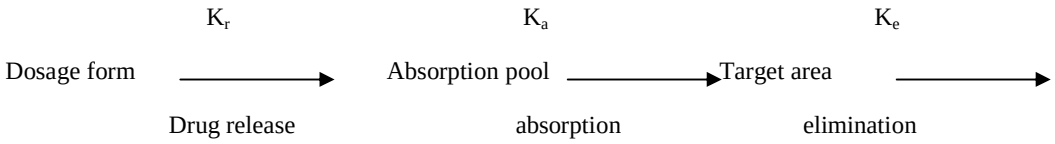
1.1 Controlled Release Drug Delivery System

In this system over the past 30 years, as the expense and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems[1].The attractiveness of those dosage forms is due to awareness to toxicity and other properties of drugs when administered or applied by conventional method in the form of tablets,capsules,injectables,ointments etc.Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency[2-4]. These factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing controlled delivery system is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery[6,7]. So controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined

pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery[8].

1.2 **Release Rate and Dose Consideration**

As already mentioned, conventional dosage forms include solutions, capsules, tablets, emulsion etc.These dosage forms can be considered to release their active ingredients into an absorption pool immediately[5]



The absorption pool represents a solution of the drug at the site of absorption.

Where

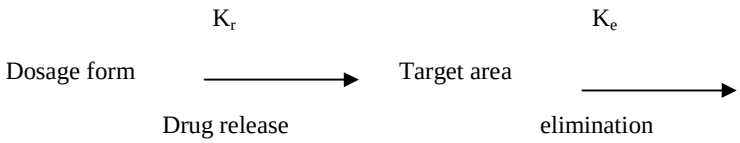
K_r - First order rate constant for drug release

K_a - First order rate constant for drug absorption

K_e -First order rate constant for overall drug elimination

For immediate release dosage forms $K_r >>> K_a$ or alternatively absorption of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area.

For non-immediate release dosage forms, $K_r >>> K_a$ that is release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to



Thus, the effort to develop a delivery system that release drug slowly must be directed primarily at altering the release rate by affecting the value of K_r.

The ideal goal in designing a controlled-release system is to deliver drug to the desired site at a rate according to needs of the body, i.e. a self-regulated system based on feedback control but this is a difficult assignment[11,12].

The pivotal question is at what rate drug should be delivered to maintain a constant blood drug level[9,10]. This constant rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at constant rates just equal to its rate elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. That is, release from the dosage form should follow zero order kinetics, as shown by

$$K_r^0 = \text{Rate in} = \text{Rate out} = K_e . C_d . V_d$$

Where

$\mathbf{K_r^0}$ = Zero order rate constant for drug release (amount/time)

$\mathbf{K_e}$ = First order rate constant for overall drug elimination ($time^{-1}$)

$\mathbf{C_d}$ =Desired drug level in the body (amount/Volume)

$\mathbf{V_d}$ =Volume space in which the drug is distributed

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage forms generally consist of two parts: an initial primary dose, D_i, Which releases drug immediately and a maintenance or sustaining dose, D_m.[13,14]

The total dose, W, thus required for the system is $W= D_i + Dm$

To maintain drug blood levels within the therapeutic range over the entire time course of therapy, most controlled-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses[15,16]. For an ideal controlled –release system that release drug by zero order kinetics, the multiple dosing regimens is analogous to that used for a constant intravenous infusion. For that controlled-release system having release kinetics other than zero-order, the multiple-dosing regimen is more complex[11]

2. MATERIALS

Alfuzosin hydrochloride BP gift sample collected in Dr.Reddy's Laboratories other ingredients were purchased on Analytical grades Microcrystalline cellulose USP-NF (Celphere 203), Hypromellose 3cps USP-NF (Methocel E3LV), Ethyl cellulose aqueous dispersion USP-NF (Aqua coat ECD30), Hydroxy prophyl methyl cellulose (HPMC) K100M USP-NF, Hypromellose (HPMC) K4 M BP.

2.1 FORMULATION PROCEDURE

To develop the three stager of formulation procedures Drug loading, Polymer is coating and Tablet preparation.

Drug loading: Dissolve Hydromellose 3cps in certain amount of water and stir till clear solution is obtained. Dissolve Alfuzosin Hcl in certain amount of water and stir clear solution is obtained. Add step two to step one and mix for 10 min and filter through#200 nylon cloth. Sifting of celphere 203 through #50/100 mesh (50 mesh passings and 100 mesh retains.

Polymer is coating: To the aqua coat ECD 30 dispersion add triethyl citrate and stir for 15mts.To step 1 add required quantity of water and filter through#200 nylon cloth. Coat the dispersion of step 2 to the drug loaded pellets in a FBC (approx 12.0-19.05% w/w build up).After sufficient drying the polymer coated pellets are sifted through # 30/80 mesh.

Tablet preparation: Sift HPMC K 100 K4M, Lactose DT and MCC 114 through #100 mesh and mix thoroughly. Dissolve plasdone K 90D in IPA a while stirring. Add step 2 to step 1 and granulate in a drier till the LOD at 105℃ is less than 3.0%.Sift the dried granules through #30 mesh. Blend the polymer coated pellets and the sifted granules of step 5 in a blender for 20 min.Pass Magnesium stearate through #80 mesh and add to step 6.Continue the blending for 5mts and finally compress the blend using 10mm round shaped Flat faced bevelled edges)punches.

Table 1: Formulation formula

INGREDIENT Qty /Tablet (mg)	B1	B2	B3	B4	B5	B6
Drug Coating						
Alfuzosin Hcl	12.055	12.096	12.085	12.105	12.085	12.095
Celphere 203	70.40	70.40	70.40	70.40	70.40	70.40
Hypromellose 3cps	4.32	4.32	4.32	4.32	4.32	4.32
Purified water	-	-	-	-	-	-
Polymer Coating						
Drug loaded pellets	83.00	83.20	83.42	83.81	83.33	83.80
Aqua coat ECD 30	45.66	45.66	45.66	45.66	45.66	45.66
Triethyl citrate	2.00	2.00	2.00	2.00	2.00	2.00
Purified water	-	-	-	-	-	-

BLENDING FIXED PARAMETERS	LIMITS	COMPRESSION FIXED PARAMETERS	LIMITS
Blending capacity	400 Lts	Type of compression machine	11 station D type
Blender RPM	8	Variables Considered for Study:	
Variables Considered for Study	Blending Time	Precompression	
Time intervals studied	20 -25 mts	Content uniformity	90-110%
Measurable Response	Content uniformity,	Assay Weight variation	100 ± 10% 450mg

Granulation and Blending Material:						
Alfuzosin polymer coated pellets	100.0	100.0	100.0	100.0	100.0	100.0
HPMC K 100M	35.00	35.00	35.00	35.00	35.00	35.00
HPMC K 4M	141.00	141.00	141.00	141.00	141.00	141.00
MCC 114M	95.00	95.00	95.00	95.00	95.00	95.00

BATCHES	**DRYING TIME mts**	**INLET TEMP (°C)**	**OUT LET TEMP (°C)**	**LOD (%W/W)**
B1-B6	0	-	-	-
B1-B6	30	52.4	36.2	5.71
B1-B6	60	62.6	42.9	4.55
B1-B6	90	64.6	44.4	4.10
B1-B6	120	65.0	47.2	3.90
B1-B6	150	65.0	49.3	2.30

Lactose DT	32.00	32.00	32.00	32.00	32.00	32.00

Table 2. Formulation process parameters

Drying Profile of Granules

DRYING FIXED PARAMETERS	**CONDITION**
Total drying time	130 mts
Avg LOD	2.362%W/W
Residual Solvent	1044ppm
Remarks	Reduced residual solvents

	Assay, water content	hardness	4-12kp
Acceptance Criteria	C.U:90-110%	Dissolution(24hrs)	79%
Batches taken for study	B1 to B6		

3. EVALUTION AND RESULTS

3.1 Evaluation of physical characteristics[16]

The formulated tablets were evaluated for the following physicochemical parameters,

Thickness

Thickness mainly depends on die filling, physical properties of material to be compressed under compression force[17, 18]. There can be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness was measured using vernier calipers.

Hardness

Tablet requires certain amount of strength or hardness, measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and evaluated for hardness during manufacturing and Hardness was expressed in $Kg/cm^{2.}$.

Friability

Friability was performed by using Roche friabilator, normally pre weighed twenty tablets were placed in the plastic chamber of the friabilator[19, 20]. This was then operated for 100 revolutions. Tablets dropping from a distance of six inches for each revolution. Tablets are then de-dusted and reweighed. Loss of less than 1% in weight is considered to be acceptable.

$$F(\%) = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

Weight variation test[21,22]

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table.

Assay of Tablet

Parameters	Formulation batches					
	B1	B2	B3	B4	B5	B6
Bulk density	0.434	0.416	0.433	0.473	0.455	0.439
Angle of Repose(°)	30°	32°	30°	31°	33°	32°
Compressibility index (%)	17.4	17.7	18.1	17.4	17.8	17.8
Water content	2.7	2.8	2.5	2.7	2.4	2.7
Sieve analysis(% retains) 100	69.9	66.8	69.3	68.9	68.9	69.9

Tablet Evaluation Test	Formulation batches					
	B1	B2	B3	B4	B5	B6
Weight variation	8.956	8.466	8.463	8.986	8.936	8.933
Hardness	4.8	4.7	4.4	4.7	4.5	4.6
Thickness	4.77	4.73	4.82	4.74	4.64	4.69
Friability	NIL	-	-	-	-	-

Content uniformity	105.6	106.6	106.5	105.9	106.2	105.6
Assay (%)	102.3	104.2	100.8	102.8	100.5	104.7

Time Point(hrs)	**Dissolution Profile of Batches**					
	50rpm					
	B1	**B2**	**B3**	**B4**	**B5**	**B6**
0	0	0	0	0	0	0
1	11.2	10.6	11.6	11.2	11.5	12.2
4	27.5	29.5	26.9	28.5	29.5	30.5
8	66.3	69.7	67.1	65.8	64.8	69.5
12	79.2	75.5	76.3	79.2	74.2	79.7
16	84.3	86.4	87.2	88.4	89.1	88.2
24	98.5	96.7	98.3	99.2	98.4	98.7

Stability studies[24]:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The selected batches were charged on accelerated stability as per ICH guidelines.

Table--: Storage condition

S.NO.	STUDY	STORAGE CONDITION
1.	Long term	25°C±2°C/60%RH±5%RH
2.	Intermediate	30^{o} C±2^{o}C/60%RH±5%RH
3.	Accelerated	40°C±2°C/75%RH±5%RH

Stability studies of selected formulations:

Stability studies were conducted for both formulations. The storage conditions used for stability studies were accelerated condition (40°C±2°C/75%±5%RH) and ambient temperature (30°C±2°C/65%±5%RH). Sample of tablets was analyzed after 2 months. Test for physical parameters (Weight variation, Hardness, friability, Thickness, and Content uniformity), Assay and Dissolution release studies.

Tablet Evaluation Test	**Formulation batches**					
	B1	B2	B3	B4	B5	B6
Weight variation	8.956	8.466	8.463	8.986	8.936	8.933
Hardness	4.8	4.7	4.4	4.7	4.5	4.6
Thickness	4.77	4.73	4.82	4.74	4.64	4.69
Friability	NIL	-	-	-	-	-
Content uniformity	105.6	106.6	106.5	105.9	106.2	105.6
Assay (%)	102.3	104.2	100.8	102.8	100.5	104.7

Time	**Dissolution Profile of Batches**
	50rpm

Point(hrs)	B1	B2	B3	B4	B5	B6
0	0	0	0	0	0	0
1	11.2	10.6	11.6	11.2	11.5	12.2
4	27.5	29.5	26.9	28.5	29.5	30.5
8	66.3	69.7	67.1	65.8	64.8	69.5
12	79.2	75.5	76.3	79.2	74.2	79.7
16	84.3	86.4	87.2	88.4	89.1	88.2
24	98.5	96.7	98.3	99.2	98.4	98.7

4. Conclusion

The present study was undertaken with an aim to optimize various critical steps of the manufacturing process of Alfuzosin Hydrochloride controlled release tablets in small scale. These formulation process converts pilot studies in future. During scale up study various critical process steps of the manufacturing process like drug loading, polymer coating, Granulation, Drying, Blending, compression and packing were standardized. And also various process variables of all the above steps were optimized. All the analytical tests performed during the entire course of the manufacturing process were found to be satisfactory and well within the acceptable limits. Finally, by analyzing the data obtained from the scale up report it can be concluded that the overall manufacturing processes are standardized with all the process variables studied showing consistent and reproducible results.

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