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FORMULATION AND EVALUATION OF FLOATING TABLET OF ALFUZOSIN HCL

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Abstract:
The present work was to prepare and optimized floating tablet of Alfuzosin HCl. Alfuzosin HCl is an alfa-1 adrenergic receptor blocker for the treatment of benign prostatic hyper pleasia & hypertension which are design to increase the gastric residence time, thus prolonging the drug release. Alfuzosin HCL has the short biological half - life (3-5hrs) the dose may range from 2.5mg thrice a day to maximum of 10mg once a day which results into inconveniency to the patients. By preparing the floating tablets of Alfuzosin HCl that deliver the drug for longer time, reduced dosage frequency & better patient compliance. The tablets were prepared by direct compression method by using different polymers like HPMC K4M, carbapol 934, xanthum gum, guar gum, sodium bicarbonate & citric acid as gas generating agent with magnesium stearate, micro crystalline cellulose & talc as lubricants and glidant respectively. All the batches were evaluated for pre compression & post compression parameters and results were in the limits. All the batches exhibited appropriate floating lag time with in prescribed limits (<r3 minutes). Formulation F14 was selected as an optimum formulation as it shows 98.8 % drug elease at the end of 12 hours. Dissolution data were fitted to various models to acertain kinetic drug release.

Key words: *Alfuzosin HCl ,HPMCK4M, xanthum gum, guar gum, carbapol 934 , sodium bicarbonate citric acid, magnesium sterate, micro crystalline cellulose& talc*

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INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form involves varying extents of optimization of dosage form characteristics with in the inherent constraints of GI physiology. Therefore a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Pharmaceutical product designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/ immediate absorption[1]. Most conventional oral drug product, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption

Rationale for oral Controlled Drug Delivery Systems

Drug administration has come of age during the past decades with many interesting devices and approaches utilized for achieving a controlled input of drug into blood pool. Especially for oral use dosage forms are enteric coated to specially design once a day formulation, have been developed for this purpose. Usually, such once a day or twice day preparations deliver drug through Gastrointestinal tract (GIT).

REVIEW OF LITERATURE:

M.R. Jimenez-Castellanos et al have worked for design and testing *in vitro* of a bioadhesive and floating drug delivery system of sotalol hydrochloride for oral administration.[43] The floating and controlled release properties of tablets consisting of cellulosic polymers were investigated. The bioadhesive property of the tablets was determined using rabbit tissue and modified tensiometer. The new oral controlled release system shows, at least *in vitro* good characteristics in relation to three parameters, controlled release of the drug, bioadhesiveness in the stomach and intestine of rabbit and buoyancy in an acidic medium

Whitehead L., Fell JT et al performed an *in vivo* study demonstrating prolonged gastric retention of floating dosage forms.[44] They compared *in vivo*behavior of multiple unit dosage form (MUDF) to a multiple unit non-floating dosage form manufactured from identical material. The result suggests that. In the fed state, this MUDF has potential for sustained drug delivery for either local or systemic purposes.

Jun Chen, William E.B. et al reported Gastric retention properties of super porous hydrogel composities.[45]They have synthesized superporous hydrogel (SPH5) which swell fast to equilibrium within minutes due to water up take by capillary wetting through numerous inter connected open pores. The mechanical strength of the highly swollen SPHs was increased by adding a composite material during the synthesis. SPH composities possessed three properties necessary for gastric retention, fast swelling, super swelling and high mechanical strength.

KouichiNakamichi et al have done evaluation of a floating dosage form of nicardipine hydrochloride and HPMC acetate succinate prepared using a twin-screw extruder.[46] They shown that the puffed dosage form, consisting of enteric polymer prepared using the twin screw extruder was very useful as a floating dosage form that was retained for a long period in the stomach.

OBJECTIVE & PLAN OF WORK

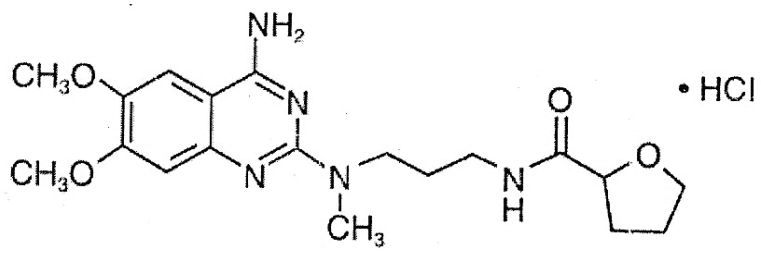
In the present work, an attempt has been made to formulate GFDDS of Alfuzosin HCl using hydroxyl propyl methyl cellulose (HPMCK4M), xantham gum, guar gum, carbapol 934 indifferent concentrations. It was also planned to develop floating tablets of Alfuzosin using a combination of HPMCK4M with xantham gum, guar gum, carbapol 934, in order to prolong the drug release and to impart floating properties to the sustained release tablet formulation.

Plan of work:

- Construction of calibration curve of ALFUZOSIN HYDROCHLORIDE.
- Preparation of HBS of ALFUZOSIN HYDROCHLORIDE floating tablets.
- PRE-COMPRESSION BLEND EVALUATION:
  - Angle of repose,
  - Bulk density,
  - Tapped density,
  - Carr's index,

- Hausner's ratio.
- EVALUATION OF TABLETS:
- Hardness,
- Thickness,
- Friability,
- Weight uniformity,
- Drug content uniformity,
- Invitro floating studies,
- Invitro drug release

DRUG PROFILE

Generic Name	:	Alfuzosin Hydrochloride
Class	:	Antihypertensive (Alpha Blockers)
Structure	:	
Chemical Name	:	N–{3-[4-Amino-6,7- dimethyoxyquinazolin-2-yl (methyl) amino] propyl} tetrahydro-2-furnamide hydrochloride
Molecular formula	:	C_{19} H_{27} N_5O_4. HCl
Molecular weight	:	425.9
Description	:	A white or almost white, slightly hygroscopic, crystalline powder.

Physico-chemical Properties

Melting point	:	240°C
Solubility	:	It is freely soluble in water, sparingly soluble in alcohol and practically insoluble in dichloromethane.
Standard	:	Alfuzosin tablets contain not less than 95% of the labeled amount of Alfuzosin HCl (C_{19} $H_{27}N_5O_4$HCl)
Packaging and storage	:	Store in a well closed container

- **Pharmacodynamics**

Mechanism of Action : It is selective α_1-adrenergic blocker. It help to release the smooth muscles in the prostate and the bladder neck making it easier to urinate and impairment in urine flow.

- **Drug interaction**
  Alfuzosin HCl have interaction with ketoconazole, itraconazole, other alpha$_1$ blockers antihypertensives, diltiazem, nitonavir.
- **Adverse Effects**
  Cardiovascular disorder, angina, hypertension, use with caution when driving and operating machinery.
- **Contraindications**
  Severe hepatic and renal impairment, intestinal obstruction, H/O postural hypotension.
- **Uses and Administration** Alfuzosin is an alpha-adrenoceptor blocker with actions similar to those of prozosin. It is used in benign prostatic hyperplasia to relieve symptoms of urinary obstruction and has been tried in the treatment of hypertension.

EXCIPIENT PROFILE:

1. Hydroxypropyl Methylcellulose (Methocel)

Chemical name: Cellulose, 2- hydroxypropyl methyl ether

Uses:

Hypromellose is widely used in oral and topical pharmaceutical formulations.

- In oral products, hypromellose is primarily used as a tablet binder, in film coating and as an extended release tablet matrix.

- Depending upon the viscosity grade, concentration of 2-20% w/w are used for film-forming solutions to film coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

2.XANTHUM GUM:

- **Chemical name**: xanthan gum
- **Non- proprietary name**:
- BP xanthan gum

Uses:

- Xanthum gum is widely used in oral and tropical pharmaceutical formulation, cosmetics and foods as a suspending and stabilizing agent.
- It is also used as thickening and emulsifying agent.

3.0Guar gum:

- **Synonym:** guar gum.

Uses:

- guar gum is an important product used in pharmaceutical formulation, cosmetic, paper,food, explosives, textiles and toiletry industries.

4.0 **Microcrystalline Cellulose**

Non-proprietary names

BP Microcrystalline cellulose

Uses:

Microcrystalline cellulose is widely used in pharmaceuticals primarily as a diluent in oral tablets and capsule formulations where it is used in both wet granulation and direct compression processes.

5.0 CARBOPOL 934

Synonym : carbomer.

Uses:

- It is used in preparation of gel, lotion and ointment.
- It is used in preparation of suspension and emulsions.

METHODOLOGY:

construction of calibration curve of alfuzosin hcl

Spectrophotometric method for the estimation of Alfuzosin Hcl

The standard calibration curve of Alfuzosin HCl was prepared in 0.1 N HCl.

Standard solution

Accurately weighed 100mg of Alfuzosin HCl was dissolved in 100ml of 0.1N HCl.

Stock solution

From the standard solution, a stock solution was prepared to give a concentration of 20µg/ml in 0.1N HCl. Aliquots of 1, 2, 3, 4 and 5ml of stock solution was pipetted out into 10ml volumetric flask. The volume was made upto the mark with 0.1N HCl. These dilutions give 2, 4, 6, 8 and 10 µg/ml concentration of Alfuzosin HCl respectively. The absorbance of prepared solution of Alfuzosin in 0.1N HCl were measured at 244.5 in Shimadzu UV -1700 spectrophotometer against an appropriate blank.

The absorbance data for standard calibration curves are given in table-3. The standard calibration curve yield a straight line, which shows that the drug follows Beer's law in the concentration range of 2-10µg/ml.

Composition of floating tablets containing HPMCK4M

Ingredients	F1	F2	F3
Alfuzosin Hcl	10 mg	10 mg	10 mg
HPMCK4M	80 mg	90 mg	100 mg
Xanthum gum	-	-	-
Guar gum	-	-	-
Carbapol 934	-	-	-
Sod.bicarbonate	60 mg	60 mg	60 mg
Citric acid	20 mg	20 mg	20 mg
Mag.stearate	5 mg	5 mg	5 mg
Talc	5 mg	5 mg	5 mg
MCC	320 mg	310 mg	300 mg

Composition of floating tablets containing XANTHUM GUM

Ingredients	F4	F5	F6
Alfuzosin Hcl	10 mg	10 mg	10 mg
HPMCK4M	-	-	-
Xanthum gum	60 mg	80 mg	100 mg
Guar gum	-	-	-
Carbapol 934	-	-	-
Sod.bicarbonate	60 mg	60 mg	60 mg
Citric acid	20 mg	20 mg	20 mg
Mag.stearate	5 mg	5 mg	5 mg
Talc	5 mg	5 mg	5 mg
MCC	340 mg	320 mg	300

Composition of floating tablets containing GUAR GUM

Ingredients	F7	F8	F9
Alfuzosin Hcl	10 mg	10 mg	10 mg
HPMCK4M	-	-	-
Xanthum gum	-	-	-
Guar gum	60 mg	80 mg	100 mg
Carbapol 934	-	-	-
Sod.bicarbonate	60 mg	60 mg	60 mg
Citric acid	20 mg	20 mg	20 mg
Mag.stearate	5 mg	5 mg	5 mg
Talc	5 mg	5 mg	5 mg
MCC	340 mg	320 mg	300 mg

Composition of floating tablets containing CARBAPOL 934

Ingredients	F10	F11
Alfuzosin Hcl	10 mg	10 mg
HPMCK4M	-	-
Xanthum gum	-	-
Guar gum	-	-
Carbapol 934	60 mg	80 mg
Sod.bicarbonate	60 mg	60 mg
Citric acid	20 mg	20 mg
Mag.stearate	5 mg	5 mg
Talc	5 mg	5 mg
MCC	340 mg	320 mg

Composition of floating tablets containing combination of HPMCK4M WITH XANTHUM GUM, GUAR GUM, CARBAPOL 934

Ingredients	F12	F13	F14
Alfuzosin Hcl	10 mg	10 mg	10 mg
HPMCK4M	50 mg	50 mg	50 mg
Xanthum gum	50 mg	-	-
Guar gum	-	50 mg	-
Carbapol 934	-	-	50 mg
Sod.bicarbonate	60 mg	60 mg	60 mg

Citric acid	20 mg	20 mg	20 mg
Mag.stearate	5 mg	5 mg	5 mg
Talc	5 mg	5 mg	5 mg
MCC	300 mg	300 mg	300 mg

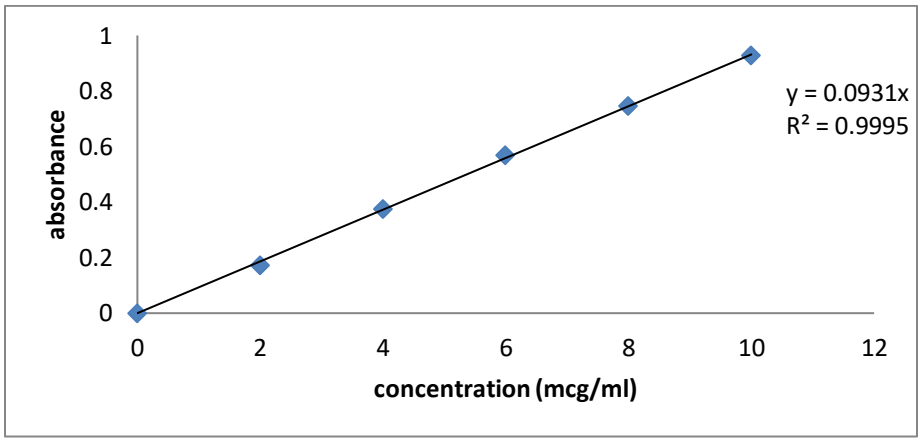
RESULTS& DISCUSSION:

Standard graph of Alfuzosin HCL

The standard graph of Alfuzosin HCL has shown good linearity with R^2 values 0.9992 in 0.1N HCL which suggests that it obeys the ‘‘Beer-Lambert’s Law’’.

TABLE: Standard graph of Alfuzosin HCL

S.NO	CONC	ABSORBANCE ± SD
1	0	0.000 ± 0.000
2	2	0.171 ±0.0020
3	4	0.3746 ±0.003
4	6	0.5676 ±0.0032
5	8	0.745 ±0.0012
6	10	0.9286 ±0.0011



Standard graph of Alfuzosin Hcl in 0.1N Hcl

Physical Evaluation of Floating Tablets

Formulation code	Hardness (kg/cm^2) ± S.D	Thickness (mm) ± S.D	Weight (mg) ± S.D	Friability (%) ± S.D	Drug content (%) ± S.D
F1	5.50±0.44	5.22±0.17	519.8±1.48	0.36±0.01	98.25±1.37
F2	7.50±0.31	5.37±0.25	500.4±0.54	0.39±0.01	95.28±0.80
F3	6.58±0.40	5.14±0.80	506±0.41	0.43±0.03	99.12±2.47
F4	7.25±0.57	5.38±0.66	520±1.14	0.44±0.02	100.24±1.25
F5	5.0±0.30	5.33±0.25	511±0.83	0.48±0.03	99.53±1.87
F6	7.5±0.57	5.24±0.71	499.9±0.67	0.34±0.01	98.8±1.99
F7	6.41±0.60	5.32±0.89	515.0±0.43	0.37±0.02	95.35±1.14
F8	5.50±0.44	5.38±0.73	520.5±0.80	0.37±0.01	96.34±2.18
F9	5.00±0.31	5.20±0.68	512.2±0.83	0.42±0.01	97.29±0.98
F10	6.08±0.37	5.48±0.88	502.1±0.93	0.48±0.03	97.35±0.43
F11	5.41±0.70	5.21±0.36	518.2±0.97	0.15±0.01	98.88±0.88

F12	7.33±0.50	5.26±0.46	505.2±0.83	0.27±0.02	96.7±1.22
F13	5.58±0.57	5.48±0.38	502.2±0.92	0.29±0.02	98.5±2.09
F14	5.75±0.77	5.25±0.37	499.0±1.22	0.33±0.03	99.54±2.15

In-Vitro drug release of Alfuzosin HCL from floating tablets containing HPMC K4M.

Time (hrs)	F1± S.D	F2± S.D	F3± S.D
0	0	0	0
1	40±1.22	33.1±0.78	20.5±1.03
2	50.4±0.37	45.8±0.66	36.9±0.87
3	64.8±0.96	56.4±0.53	46.2±0.56
4	81±0.74	66.8±0.34	49.1±0.45
6	83.7±1.22	71.5±0.18	57.6±0.79
8	87.3±0.87	73.3±0.77	64.6±0.34
10	96.8±0.54	99.4±0.89	87.3±0.45
12	96.8±0.39	99.9±0.47	97.1±0.74

***In vitro* floating of** Alfuzosin **HCl**

Formulation code	Floating lag time (sec)	Total floating time
F1	25 sec	6.5 hrs
F2	29Sec	8 hrs
F3	37Sec	12 hrs
F4	48Sec	12 hrs
F5	24Sec	8 hrs
F6	37Sec	12 hrs
F7	20Sec	9.5 hrs
F8	15Sec	12 hrs
F9	12Sec	12 hrs
F10	48Sec	11.5 hrs
F11	37Sec	12 hrs
F12	25Sec	12 hrs
F13	38Sec	12 hrs
F14	23Sec	12 hrs

Drug Release Kinetics of Alfuzosin HCL floating Formulations

Formulations	Zero order R^2	Zero order K_0	First order R^2	First order K_1	Korsmeyer – peppas R^2	Korsmeyer – peppas N	Higuchi R^2
F1	0.589	2.87	0.9471	0.139	0.931	0.28	0.847
F2	0.756	3.10	0.929	0.193	0.971	0.331	0.944
F3	0.823	3.15	0.948	0.112	0.993	0.376	0.9767
F4	0.955	3.72	0.904	0.149	0.976	0.53	0.969
F5	0.860	3.38	0.897	0.196	0.971	0.360	0.975
F6	0.862	3.36	0.960	0.139	0.989	0.381	0.986
F7	0.755	3.16	0.945	0.182	0.968	0.316	0.948
F8	0.744	2.68	0.951	0.075	0.991	0.291	0.936
F9	0.874	3.53	0.936	0.174	0.992	0.439	0.991
F10	0.916	3.60	0.931	0.161	0.997	0.446	0.995
F11	0.963	3.66	0.910	0.13	0.983	0.543	0.972
F12	0.899	3.43	0.968	0.112	0.987	0.476	0.991
F13	0.962	3.72	0.900	0.145	0.966	0.532	0.964
F14	0.952	3.78	0.895	0.171	0.988	0.543	0.982

SUMMARY:

- Floating tablets of Alfuzosin HCL were prepared using polymers like HPMC K4M, xanthum gum, guar gum, carbapol 934.
- The formulated batches were evaluated for physical parameters and dissolution profiles. The physical properties like weight variation and friability of all batches complied with the pharmacopeia specifications. The drug content of all tablet was in the range of 95-103%.
- It was observed that the increasing concentration of polymers had a retarding effect on the drug release from the polymer matrices.

CONCLUSION:

The HPMC K4M in combination with other polymers is having more prominent role in drug release. The stable extended-release floating tablets which can control drug release up to 12 hours of Alfuzosin Hcl can be prepared by adjusting the concentration of binary polymers. Finally, it may be concluded that this novel drug delivery system i.e floating system offers a valuable dosage form which delivers the drug at a controlled rate and at a specific site. The floating system of Alfuzosin HCL provides the better options for increasing the bioavailability and reliability for hypertension and in benign prostatic hyperplasia to relieve symptoms of urinary obstruction by allowing a better control of fluctuations observed with conventional dosage forms. Formulation F13 appears suitable for further pharmacodynamic and pharmacokinetic studies to evaluate clinical safety of these floating system in suitable animal and human models.

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