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RESEARCH ARTICLE

FORMULATION AND *IN-VITRO* EVALUATION OF FLOATING DRUG DELIVERY SYSTEM FOR FLUCLOXACILLIN

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ABSTRACT

In the present research work gastro retentive floating matrix formulation of flucloxacillin by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformulation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulation prepared with Guar gum retarded the drug release up to 12 hours in the concentration of 45 mg (F9).The optimized formulation was subjected to invivo studies. From the results of *In vivo* studies conducted between final optimized formulation and marketed formulation of, it can be concluded that bioavailability of final optimized formulation was higher than the marketed formulation as well as pure drug.

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INTRODUCTION

Flucloxacillin magnesium is an isoxazolyl penicillin containing ß-lactam group of antibiotic which shows a bactericidal effect upon many gram positive organisms including ß-lactamase producing staphylococci and streptococci (1). Flucloxacillin magnesium is stable in acidic medium and not inactivated by staphylococcal ß-lactamases. The mechanism of action is by interfering with bacterial cell wall synthesis by targeting Penicillin Binding Protein (PBP). Flucloxacillin is effective in the treatment of infections caused by penicillin-resistant staphylococci, which is the sole indication for its use because other penicillins like benzyl penicillin are not resistant to staphylococci producing penicillinase or β-lactamases. Flucloxacillin is not inactivated by staphylococci-producing penicillinases and it is used for the treatment to skin and soft tissue infections and respiratory tract infections.

MATERIALS AND METHODS

Flucloxacillin, Microcrystalline cellulose, Chitosan, Guar gum, Sodium CMC, HPMC K4M , HPMCK 15M, HPMC K100M , Magnesium stearate, Di sodium glycine carbonate, Talc all the chemicals were laboratory grade.

Formulation Development of Tablets: All the formulations were prepared by direct compression. The compressions of different formulations are given in Table 1.The tablets were prepared as per the procedure given below and aim is to prolong the release of Flucloxacillin. Total weight of the tablet was considered as 300 mg.

Procedure:

- Flucloxacillin and all other ingredients were individually passed through sieveno 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method.

Optimizations of Di Sodium Glycine Carbonate Concentration: Di sodium glycine carbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of Di sodium glycine carbonate were employed; floating lag time and floating duration were observed. Based on that the concentration of Di sodium glycine carbonate was finalized and preceded for further formulations.

Table 1. Optimization Di Sodium Glycines Carbonate Concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Flucloxacillin	125	125	125
2	Guar gum	30	30	30
4	Di sodium glycine carbonate	30	60	90
5	Mg.Stearate	5	5	5
5	Talc	5	5	5
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	300	300	300

All the quantities were in mg. Based on the floating lag time and floating duration the concentration of Di sodium glycine carbonate was optimised. All the quantities were in mg, total weight is 300 mg.

RESULTS AND DISCUSSION

***In Vivo* Studies**

Materials: Disodium hydrogen orthophosphate and Potassium dihydrogen ortho phosphate, Methanol and distilled water. All reagents and chemicals used were of analytical grade. The pure powders of amoxicillin trihydrate (assay: 99.60%) and flucloxacillin sodium (99.80%) were obtained from merck Specialities, Mumbai India.

of flucloxacillin sodium in capsule dosage form,World Journal of Pharmacy and Pharmaceutical Sciences, Vol 5, Issue 4, 2016.

Materials: HPLC grade acetonitrile, orthophosphoric acid, and all other chemicals were purchased from Rankem chemical division, Hyderabad. HPLC grade water was used throughout the study.

Instrumentation: HPLC instrument used was of WATERS HPLC 2695 SYSTEM with auto-injector and PDA detector. Software used was Empower 2. UV VIS spectro photo meter PG Instruments T60 with special bandwidths of 2 mm and 10 mm and matched quartz was used for measuring absorbance for bumetanide solutions.

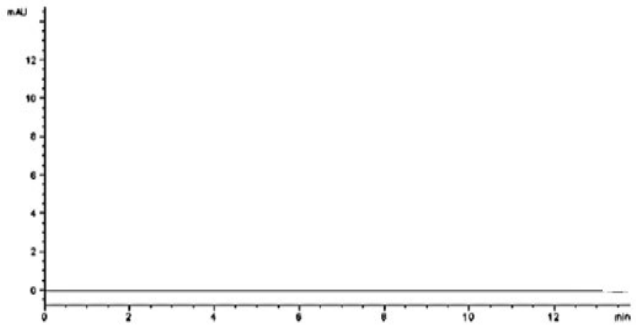

Fig. 1. HPLC Blank Chromatogram for Flucloxacillin

Table 2. Formulation Composition for Floating Tablets

Formulation No.	Flucloxacillin	Sodium CMC	Chitosan	Guar gum	Di sodium glycine carbonate	Mag. Stearate	Talc	MCC pH 102
F1	125	15	-----	-----	30	5	5	QS
F2	125	30	-----	-----	30	5	5	QS
F3	125	45	-----	-----	30	5	5	QS
F4	125	-----	15	-----	30	5	5	QS
F5	125	-----	30	-----	30	5	5	QS
F6	125	-----	45	-----	30	5	5	QS
F7	125	-----	-----	15	30	5	5	QS
F8	125	-----	-----	30	30	5	5	QS
F9	125	-----	-----	45	30	5	5	QS

Table 3. Formulation Composition for Floating Tablets

Formulation No.	FLUCLOXACILLIN	HPMC K4M	HPMC K15M	HPMC K100M	Di sodium glycine carbonate	Mag. Stearate	Talc	MCC pH 102
F10	125	15	-----	-----	30	5	5	QS
F11	125	30	-----	-----	30	5	5	QS
F12	125	45	----	-----	30	5	5	QS
F13	125	-----	15	-----	30	5	5	QS
F14	125	-----	30	----	30	5	5	QS
F15	125	-----	45	-----	30	5	5	QS
F16	125	-----	-----	15	30	5	5	QS
F17	125	-----	-----	30	30	5	5	QS
F18	125	-----	-----	45	30	5	5	QS

Chromatographic Conditions for Flucloxacillin

Column: Phenomenex ® Bondclone 10 C18 (300×3.9 mm, 5µm)
Flow rate: 1.00 ml/min

Mobile phase: 60% Methanol: 40% KH2PO4 buffer (pH=5 adjusted with 1M sodium Hydroxide solution)

Wavelength of Detection: 225nm

Retention Time: 17.36 mins

Temperature: ambient (about 25ºC)

Injection volume: 100 µl

Reference: Michael Worlako Klu*, Bright Selorm Addy and David Ntinagyei Mintah, a simple validated rp- hplc method for the analysis

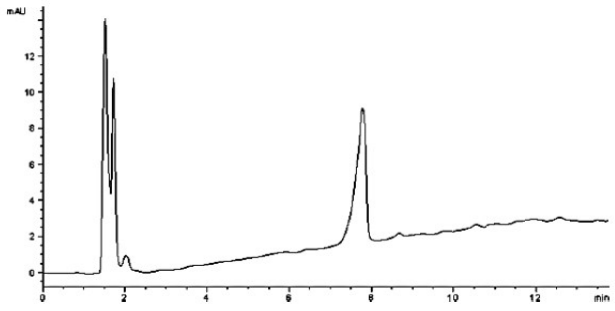

Fig. 2. HPLC Chromatogram of Flucloxacillin in Rabbit Plasma

Different pharmacokinetic parameters were calculated in each rabbit by using software KINETICA 2000 (Version 3.0) and are given in Table 5. Various pharmacokinetic parameters include C_{max}, T_{max}, AUC (Area under the Curve) and relative bioavailability.

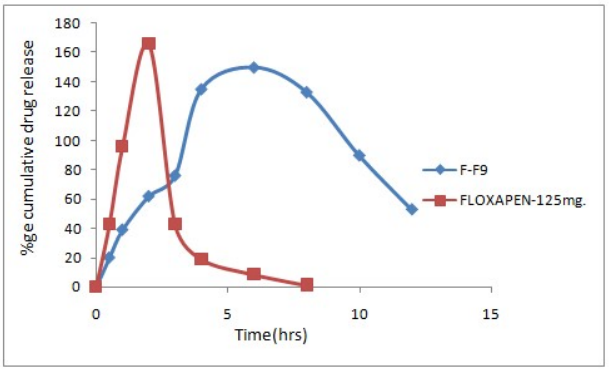

Fig 3. In Vivo Drug Release of the Formulations and Marketed Products

Table 4. Plasma Concentration Values of optimized Formulation

Time (hrs)	Plasma Concentration (ng/mL)	
	F-F9	FLOXAPEN-125mg.
0	0	0
0.5	19.8 ± 4.5	42.5 ± 5.6
1	38.9 ± 6.5	95.8 ± 6.8
2	61.8 ± 7.8	165.8 ±12.6
3	75.9 ± 7.5	42.5 ± 11.5
4	134.9 ± 14.5	18.9 ± 10.6
6	149.8 ± 26.8	8.5 ± 5.4
8	132.9 ± 16.7	1.2 ± 1.1
10	89.7 ± 11.2	--
12	52.8 ± 5.6	--

Table 5. Pharmacokinetic Parameters of Piretanide Formulations

Pharmacokinetic Parameter	Value	
	F-F9	FLOXAPEN-125mg.
C_{max}(ng/ml)	167.3 ± 10.8	174. 3 ± 5.7
T_{max}(hrs)	7.9 ± 2.4	1.6 ± 0.8
K_{el}(hr^{-1})	0.089	0.495
$t_{1/2}$ (hrs)	7.84	1.39
Ka (hr^{-1})	0.459	0.519
MRT (hrs)	9.27	3.93
AUC (ng.hr/ml)	2963.87	553.12
Relative Bioavailability	5.35	1.00

Summary

In the present research work gastro retentive floating matrix formulation of flucloxacillin by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers.

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