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Control the drug release of Levofloxacin by using different sustained release polymers in matrix tablets

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Abstract

The present study is aimed to control the drug release, of slightly water soluble drugs like Ofloxain. It is a slightly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. In this study an attempt was made to sustain the in vitro dissolution profiles of Ofloxain by using various sustained release polymers like carboxyl ethyl cellulose, HPMC K100, eudragitS100, sodium alginate, chitosan etc. Drug- Polymer Interaction Studies like FTIR, DSC were performed and results showed that there were no possible interactions between the drug and our entire tablet polymer. In conclusion, results suggest satisfactory result is obtained by F6.F7, F8 formulations so this type of polymers are suitable for prepare Ofloxain sustained release tablets than more drug release is controlled by eudragit S100 from all the sustained polymers, because compare with acidic medium the Ofloxain solubility is less in base medium so eudragitS100 could potentially lead to retained the drug release in of oral Ofloxain products in acidic medium.

Keywords: Sustained release polymers, matrix formation, antibiotics. reduce dose frequency, reduce the side effects.

Introduction

The oral sustained-release tablets formulation are more helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. Than all these are comes with reasonable cost. And oral dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance[1].

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. Which includes both hydrophilic and hydrophobic polymers[2] commonly available hydrophilic polymers include Hydroxypropyl methylcellulose (HPMC) and Sodium alginate etc. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine[3].

Ofloxain is a fluoroquinolone antibiotic medicine used in adults to treat certain infections caused by bacteria. Ofloxain was less safe for works in people under 18 years of age. Children less than 18 years of age have a higher chance of getting bone, joint, or tendon problems such as pain or swelling while taking Ofloxain. oral administration, the bioavailability of Ofloxain in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved one to two hours after an oral dose. Absorption of Ofloxain after single or multiple doses of 200 to 400 mg is predictable, and the amount of drug absorbed increases proportionately with the dose. Ofloxain has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4-5 hours and 20-25 hours. However, the longer half-life represents less than 5% of the total AUC. Accumulation at steady-state can be estimated using a half-life of 9 hours[4]. The total clearance and volume of distribution are approximately similar after single or multiple doses. Elimination is mainly by renal excretion. The following are mean peak serum concentrations in healthy 70-80 kg male volunteers after single oral doses of 200, 300, or 400 mg of Ofloxain or after multiple oral doses of 400 mg.

Experimental

Materials

Ofloxain was obtained as a gift sample from celestial labs, Hyderabad, india. Sodium Starch Glycolate, Crosspovidone, and Crosscarmellose were gift samples from celestial labs, Hyderabad, India. All other chemicals used were of analytical grade.

Methods

Preparation of polymeric matrix tablets of Ofloxain

Different formulations of Ofloxain (celestial labs) matrix tablets was prepared with different types of the polymers that was carboxyl ethyl cellulose and HPMC K100, eudragitS100, sodium alginate, chitosan etc. The drug with any one sustained release polymer and other ingredients croscarmellose, corn starch, ironoxide, polyethylene glycol, lactose monohydrate (celestial labs) was designed and prepared by wet granulation method[5]. All the materials were weighed accurately and passed through a 35-mesh sieve. And add PVP than the mixing was performed in a cubic mixer (Erweka, Germany) prepared granules by pass the dump mass though the 16-mesh and add magnesium stearate, talc, than all formulations (containing 200 mg Ofloxain) was compressed into flat 14 mm diameter tablets, by 16 station multi compression machinery. The compression force was adjusted for each formulation so that the corresponding crushing strengths of tablets were at maximum.

Pre compression parameters

Angle of repose

It was determined by fixed funnel method. Accurately weighed quantity of blend was taken in a funnel the height of the funnel was adjusted such that the tip of the funnel just touches the apex of heap of the blend[6]. Then the blend was allowed to flow through the funnel freely on to the surface. The diameter was then measured and angle of repose was calculated by following equation.

$$\text{Tan } \theta = h/r$$

Where θ is angle of repose, h is height of the cone and, r is radius of the cone base.

Bulk density:

It was determined by pouring a weighed quantity of blend in to a graduated cylinder and measuring the bulk volume. Bulk density = weight of the powder / bulk volume

Tapped density

It was determined by pouring a known mass of blend in a measuring cylinder and tapped for fixed time. Then the final volume occupied by the blend was measured.

Tapped density = weight of the blend / final volume

Compressibility index

The compressibility index (carr's index) was measured for propensity of a powder to be compressed.

Carr's compressibility index = [(tapped density- bulk density / tapped density)] 100

Post compression parameters

Weight variation

Twenty tablets from each formulation were randomly selected and average weight was determined. Then individual tablets were weighed and was compared with average weight.

Hardness

The hardness of the tablets was determined by Monsanto hardness tester .It is expressed in kg/cm^2.

Friability

Friability of tablets was determined by Roche friabilator. Preweighed samples of tablets was placed in the friabilator and subjected to 100 revolutions. The tablets were dedusted and reweighed.

$$\text{Friability} = (1 - w_0/w) \times 100$$

Where w_0 is intial weight of tablet, w is final weight of tablet

Determination of drug content

Five tablets were powdered and the blend equivalent to 200mg of Ofloxain was weighed and dissolved in methanol/0.1N HCL buffer. The solution was then filtered, diluted and drug content was then determined by UV- Spectrophotometer at 294nm.

Invitro dissolution studies

Invitro dissolution testing was carried out using USP Apparatus I and the amount of drug released was determined by UV-Spectrophotometer at 294nm *at 50rpm in 900ml of contains 0.1 HCL maintained at 37* ± 0.5 º C. 5ml aliquot was withdrawn at the specified time intervals and replaced with fresh dissolution media then these samples were filtered through whatmann filter paper and analyzed by UV- Spectrophotometer at 294nm[7,8].

Drug- Polymer Interaction Studies

By the means of spectroscopic and thermal analysis drug-polymer interaction between Ofloxain and excipients of formulations of various techniques are conducted. These studies determine the physical stability of an drug. DSC studies were carried out on pure drug and optimized formulations and the thermo grams were obtained using DSC (Perkin-Elmer, Shelton, U.S). The analysis were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to get rid of oxidative and pyrrolytic effects at a standard

heating rate of 15ºC/minute over a temperature range of 50ºC - 350ºC. Further the infrared spectra studies of Ofloxain and optimized formulations recorded between 400 to 4000 cm^{-1} on FTIR spectrometer[9] (Perkin Elmer FTIR, Perkin Elmer Inst. USA) to detect the drug-excipient interactions using KBr disk method . The resultant spectra obtained, were compared for any possible changes in the peaks of the spectra.

Results and Discussion

Precompression parameters

The powder mixtures of different formulations were evaluated for the bulk density and tapped density values ranged from 0.324 to 0.337 and 0.382 to 0.414 respectively. The results of angle of repose and % Carr's index ranged from 26.72±3.15 to 31.36±0.79 and 11.70 to 20.85 respectively.

Table 1 Composition of different type of sustained release polymers to prepare Ofloxain matrix tablets

INGREDIENTS(mg)	M1	M2	M3	M4	M5	M6	M7	M8
Ofloxain	200	200	200	200	200	200	200	200
Carboxylmethyl cellulose	80	-	-	-	-	-	-	-
sodium alginate	-	80	-	-	-	-	-	-
cellulose acetate	-	-	80	-	-	-	-	-
sodium carboxymethylcellulose	-	-	-	80	-	-	-	-
eudragits100	-	-	-	-	80	-	-	-
carbopol 934.	-	-	-	-	-	80	-	-
chitosan	-	-	-	-	-	-	80	-
hydroxypropylmethylcellulose	-	-	-	-	-	-	-	80
lactose monohydrate	125	125	125	125	125	125	125	125
polyethylene glycol	13	13	13	13	13	13	13	13
yellow iron oxide	2	2	2	2	2	2	2	2
corn starch	10	10	10	10	10	10	10	10
PVP	10	10	10	10	10	10	10	10
croscarmellose	4	4	4	4	4	4	4	4
talc	4	4	4	4	4	4	4	4
magnesium stearate	2	2	2	2	2	2	2	2

Table 2 Characterization of powder mixture

Formulation	Angle of Repose*(^{0})	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)
M1	27.86±3.13	0.330	0.412	19.71
M2	29.42±2.96	0.333	0.410	18.85
M3	28.25±3.72	0.331	0.401	17.35
M4	27.15±3.11	0.336	0.392	14.43
M5	29.05±1.39	0.324	0.382	15.32
M6	29.70±3.92	0.336	0.387	13.21
M7	29.05±1.39	0.324	0.382	15.32
M8	29.05±1.39	0.324	0.382	15.32

Table 3 Physical properties of Ofloxain matrix tablets

Formulation	Weight variation* (mg)	Hardness† (Kg/cm^2)	Friability (%)	Drug content‡ (%)
M1	450.70±3.79	6.03±0.31	0.39	100.37±2.20
M2	450.60±3.49	6.23±0.21	0.50	99.60±1.25
M3	450.10±3.78	6.17±0.35	0.44	98.80±1.23
M4	450.65±3.44	5.93±0.25	0.27	98.02±1.34
M5	450.60±3.55	6.23±0.31	0.44	98.64±0.42
M6	450.00±4.21	6.33±0.29	0.45	98.47±1.39
M7	450.60±3.55	6.23±0.31	0.44	100.11±1.98
M8	450.60±3.55	6.23±0.31	0.44	98.37±1.68

Table 4 Dissolution data of Ofloxain matrix tablets from F1 to F5

Time (h)	Cumulative percent of Ofloxain released (Mean ± S.D.)				
	M1	M2	M3	M4	M5
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	5.090±0.55	35.15±1.48	27.85±0.40	4.26±0.34	3.72±0.15
4	14.30±0.78	94.58±2.81	85.24±1.86	11.38±0.75	10.39±0.42
6	40.56±2.54	118.46±4.57	102.22±1.18	34.49±1.27	21.52±1.05
8	59.35±2.38	-	-	45.88±0.69	34.58±1.33
10	72.69±1.53	-	-	57.28±1.78	45.41±2.54
11	86.03±3.41	-	-	74.48±1.87	51.98±2.79
12	104.99±1.46	-	-	83.50±0.70	60.40±2.36

Table 5 Dissolution data comparison of Ofloxain matrix tablets from F6 to F8

Time (h)	Cumulative percent of Ofloxain released (Mean ± S.D.)		
	M6	M7	M8
0	0.00±0.00	0.00±0.00	0.00±0.00
2	5.09±0.55	1.31±0.10	0.71±0.15
4	14.30±0.78	7.05±0.19	6.26±0.33
6	40.56±2.54	28.65±1.01	18.41±0.68
8	59.35±2.38	48.90±1.07	49.23±3.30
10	72.69±1.53	70.00±1.12	73.16±2.13
11	86.03±3.41	81.44±0.94	82.10±1.33
12	104.99±1.46	101.89±1.90	105.43±3.33

Table 6 Release kinetics of Ofloxain matrix tablets

Formulation	Zero order		First order		Higuchi	
	K_0 (mg/hr)	R^2	K_1 (hr^{-1})	R^2	K ($mg/hr^{-1/2}$)	R^2
M1	3.391	0.963	0.17733	0.797	17.05	0.872
M2	1.798	0.948	0.1566	0.755	9.246	0.897
M3	3.794	0.974	0.18885	0.814	18.84	0.860
M4	4.622	0.964	0.20266	0.801	23.01	0.855
M5	5.519	0.852	0.20497	0.598	25.34	0.889
M6	4.462	0.942	0.1543	0.633	23.46	0.932
M7	4.676	0.942	0.19576	0.772	23.78	0.849
M8	3.872	0.952	0.19806	0.812	19.33	0.85

K_0- Zero order rate constant, K_1- First order rate constant, K- Higuchi model rate constant and R^2 -Correlation coefficient

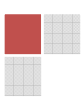


Figure 1 Release profiles from Ofloxain **matrix tablets from F1 to F5**

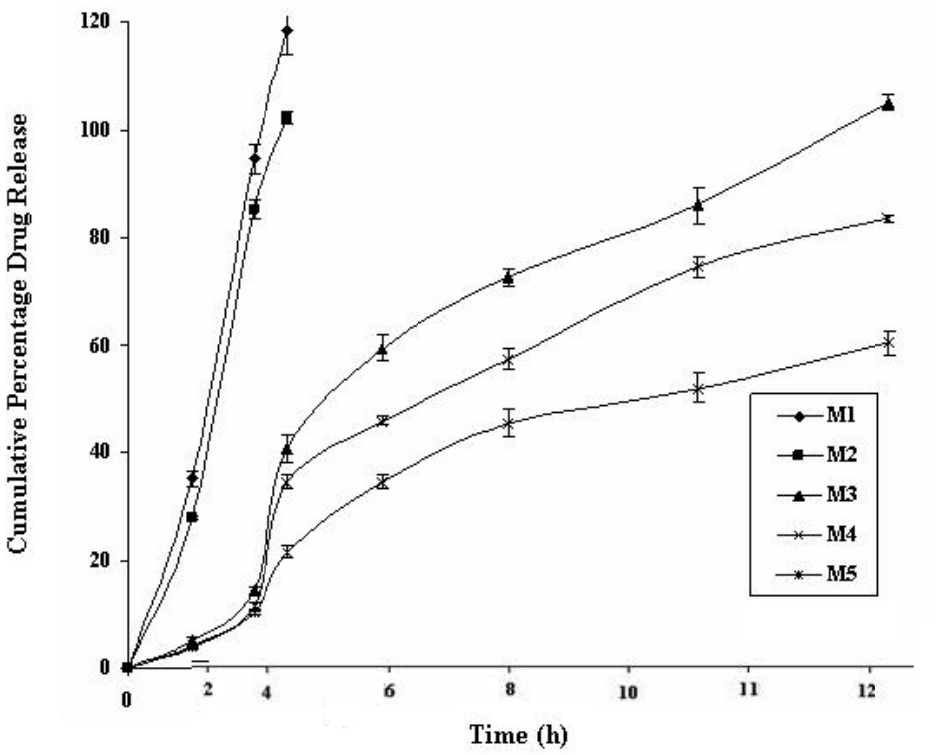


Figure 2 Comparison of release profiles of Ofloxain matrix tablets from F6 to F8

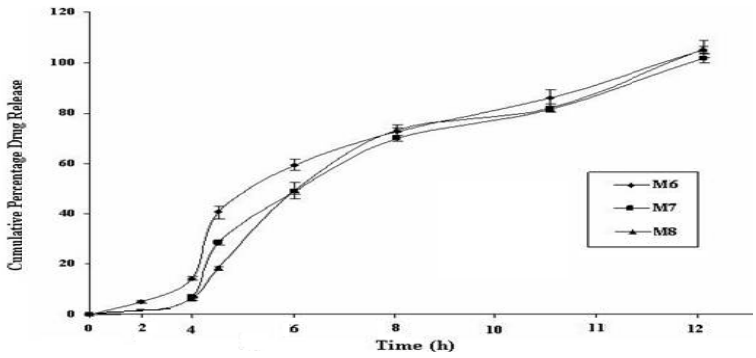


Figure.1 DSC studies of the pure drug and optimized formulations

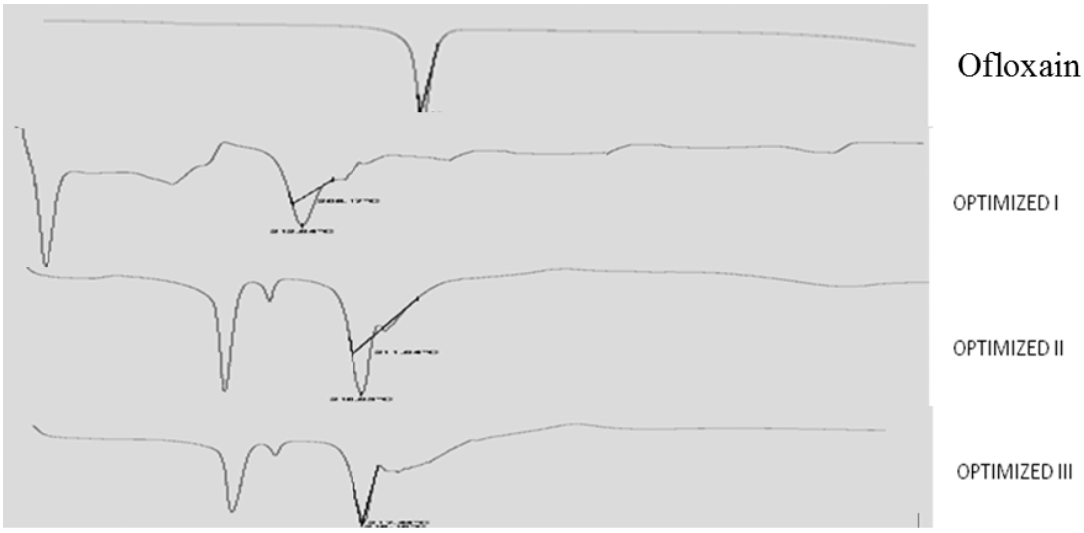
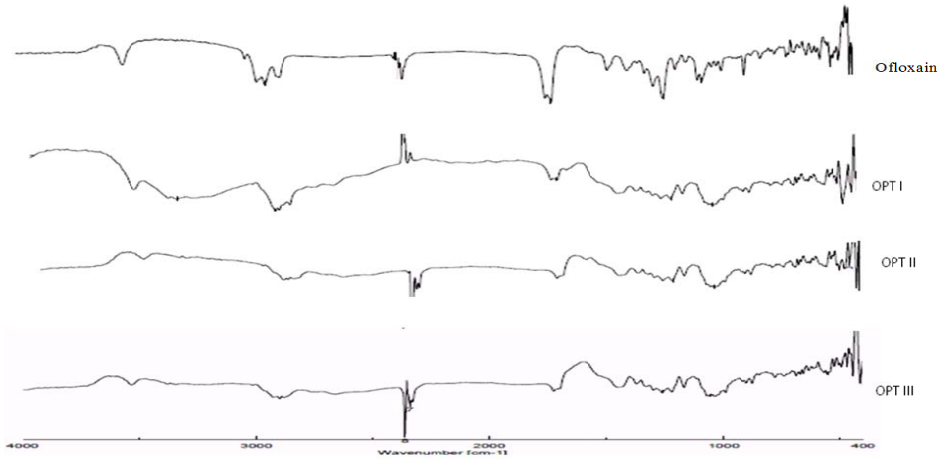


Figure.2 FTIR studies of pure drug and optimized formulations



Postcompression parameters

The physical properties of Ofloxain tablets are the average weight of tablets was found to be 450.85±2.92 mg and they were within the pharmacopoeial limits[10] The hardness of the core tablets was found to be 8.83±0.35 kg/cm2 and they were also found to comply with the friability test since the weight loss was found to be 0.58%. The core tablets thickness and diameter was found to be 3.01±0.02 mm and 7.04±0.01 mm respectively11.

In vitro dissolution study

From the cumulative mean percent of Ofloxain released from matrix tablets containing different types of sustained release polymers, incorporation of 80 mg of polymer in the total tablet weight was found to be satisfactory to formulate a tablet with good integrity .

The release profiles of Ofloxain from the matrix tablets of different types of matrix polymers was found to vary from 21.52±1.05% to 102.22±1.18%.HPMC, chitosan, carbopol 934, Carboxyl methyl cellulose drug release was increased gradually after 5 h and it was found to be 60.40± 2.23 to 104.99±1.46 % in 12 h.

Based on the in-vitro dissolution data, formulation M1, M6, M7, M8 was considered as the best one to prepare the Ofloxain matrix tablets.

In vitro release kinetics

For matrix tablets the values of K, and r2 (correlation coefficient of the regression analysis) of zero order, first order and Higuchi models of designed formulations were given in Table 6. The n values calculated for different formulations were found in the range of 1.2966 to 1.7495. The MDT values were found to be 2.70-2.21. The values of K, n, r2, and MDT from the dissolution data of designed formulations were given in Table 6.

In case of compression coated tablets, the values of K, and r2 (correlation coefficient of the regression analysis) of zero order, first order and Higuchi models of designed formulations were given in Table 6. The n values calculated for different formulations were found in the range of 1.1591 to 2.9002. The MDT values were found to be 2.35-12.62.

Drug polymer interaction studies

DSC studies were performed to understand the nature of the drug in the formulated tablets. Thermograms obtained for pure drug[12], HPMC K100, eudragitS100, sodium alginate, chitosan magnesium stearate, talc, croscarmellose ,corn starch,iron oxide, and optimized formulations of three methods were shown in Figure1 .The DSC of Ofloxain showed endothermic peaks equivalent to its melting point at 250-2570C .where as thermograms of the optimized formulations did not show any significant shift in the endothermic peak. The FTIR spectrum of above mentioned excipients and optimized formulations of three methods were compared to that of pure Ofloxain. The IR spectra were pure Ofloxain and optimized formulation.

Conclusion

Ofloxain matrix tablets were successfully formulated by using different sustained release polymers and compared the dissolution rate. From *invitro* dissolution studies it was concluded that dissolution results suggest that was satisfactory result is obtained by F6.F7,F8 formulations so this type of polymers are suitable for prepare Ofloxain sustained release tablets than more drug release is controlled by eudragit S100 from all the sustained polymers, because compare with acidic medium the Ofloxain solubility is less in base medium so eudragitS100 could potentially lead to retained the drug release in of oral Ofloxain products in acidic medium Hence, further efficacy must be assessed by performing pharmacokinetic studies in human.

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