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Formulation and Invitro Characterization of Gastro Retentive Drug Delivery System of Ofloxacin

Anil Kumar Chandragiri*[1], Ganesh Kumar Y[2], Chandana CH[3], Swetha B[4], Thirupathi Kaluvala[1]

[1]*University College of Pharmaceutical Sciences, Satavahana University, Karimnagar, A.P,India.*
[2]*Research Scholar, Faculty of Pharmaceutical Sciences, JNTU Hyderabad, A.P, India.*
[3]*Vikas college of pharmacy, Shameerpet, Jangoan, Warangal, A.P,India.*, [4]*Vivekananda Group of Institutions, Hayathnagar, R.R. Dist, A.P, India.*

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ABSTRACT

Ofloxacin is a synthetic chemotherapeutic anti-infective drug of the fluoroquinolone class, considered to be a second-generation fluoroquinolone class-II. It acts by inhibiting DNA gyrase, a type II topoisomerase and topoisomerase IV, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division. It is active against both Gram-positive and Gram-negative bacteria. Floating drug delivery system can be retained in the stomach for long time by formulating ofloxacin with low density polymers like hydroxyl propyl methyl cellulose and gas generating agents are added to the system to reduce the density of the system. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. Standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of in vitro performance for floating dosage forms. UV spectrophotometric method was developed for the Ofloxacin. The method obeys Beer's law in the concentration of 2 - 10µg/ml with regression coefficient of 0.999. Thus the said method was found to be suitable for the estimation of Ofloxacin in in-vitro dissolution studies at λ max 277nm. F6 formulation high concentration polymer had best integrity and could sustain drug release till 12hrs of dissolution study.

Key words: *Ofloxacin, Fluoroquinolone, Direct Compression, GRDDS.*

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation [1].

Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-life are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the Drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract [2].

MATERIALS AND METHODS

Ofloxacin, HPMC K4M, HPMC K15 M, Sodium Bicarbonate, Magnesium stearate, Talc and Microcrystalline Cellulose.

Methodology:

Standard curve for Ofloxacin pure drug:

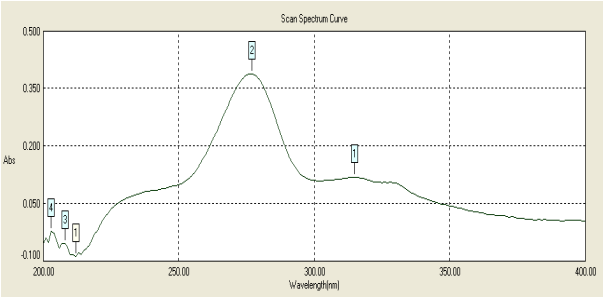
UV spectrophotometric method was developed for the Ofloxacin. The method obeys Beer's law in the concentration of 2 - 10µg/ml with regression coefficient of 0.999. Thus the said method was found to be suitable for the estimation of Ofloxacin in in-vitro dissolution studies at λ max 277nm.

***Corresponding author:**
Anil Kumar Chandragiri
University College of Pharmaceutical Sciences,
Satavahana University, Karimnagar, A.P,India.
**E-Mail: chanil123@gmail.com*

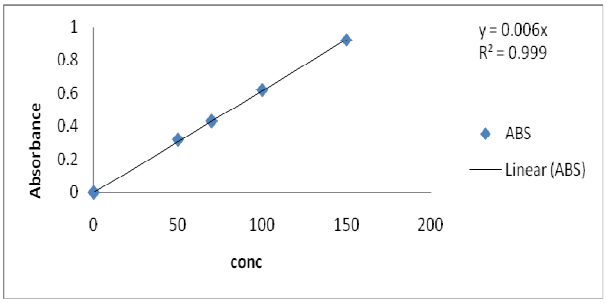
Table No. 1: Standard Graph of Ofloxacin in 0.1 N Hcl

Sl. No.	Concentration	Absorbance
1	0	0
2	50	0.365
3	70	0.490
4	100	0.665
5	150	0.920

Ofloxacin floating tablets standardization of by UV method:



(a)



(b)

Fig. 1: a) Standard graph of ofloxacin in 0.1 N HCl, b) Linearity Curve for Standard ofloxacin

Evaluation of Tablets:

Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose. 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.

$$\tan(\theta) = h / r$$
$$\theta = \tan^{-1}(h / r)$$

Where 'θ' is the angle of repose, 'h' is the height in cms,r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particals slip and roll over each other through the sides of the funnel.

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. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of powder, Vb is the bulk volume of the powder.

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 and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder,Vt is the tapped volume of the powder.

Porosity:

The voids present in the powder mass may be more significant than solid components in certain studies. A fine capillary network of voids or pores has been shown to enhance that rate of liquid uptake by the tablets which in turn increase the rate of their disintegration.

Ratio of total volume of void spaces to (Vv) to the bulk volume of material is often selected to monitor the progress of compression [3-9].

This ratio Vv/ Vb is referred to as porosity.

$$Vv = Vb - Vt$$
$$\text{Porosity } E = Vb - Vt / Vb = 1 - Vt / Vb$$

Frequently, porosity is expressed as percentage.

$$E = 100 \text{ X } [1 - Vt / Vb]$$

Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given by

$$I = Dt - Db / Dt \text{ X } 100$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = Dt / Db$$

Where, Dt is the tapped density, Db is the bulk density. Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Weight variation:

20 tablets were selected randomly from the batch and weighed individually to check for weight variation. Table -2 Weight Variation Specification as per IP Average Weight of Tablet % Deviation 80 mg or less ±10. More than 80 mg but less than 250 mg ±7.5. 250 mg or more ±5.

Hardness (or) tablet crushing strength (fc):

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/cm2.

Thickness:

The thickness of the tablets was measured using vernier caliber. It is expressed in mm.

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 I height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \text{Winitial - Wfinal / Winitial X } 100$$

Floating Test:

The time between introduction of dosage form and its buoyancy on simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time (TFT) [10-17].

Table No. 2: Precompression Parameters: Mean SD (N=3)

S. No.	Formulation	Angle of repose	Bulk density	Tapped density	Carrs index
1	F1	17.53	0.245	0.279	14.7
2	F2	17.17	0.234	0.265	12.60
3	F3	29.34	0.50	0.58	13.79
4	F4	27.91	0.45	0.55	18.18
5	F5	18.34	0.250	0.273	12.33
6	F6	17.16	0.238	0.265	14.33

Preparation of Tablets:

Method:

Ofloxacin Floating tablet by using direct compression method:

The drug and all other excipients were sifted through #40 sieves and mixed thoroughly. To above blend was pre lubricated with HPMC, MCC and lubricated with magnesium stearate. The above lubricated blend was compressed using standard flat faced punch on a sixteen station rotary tablet punching machine [18-21].

Table No. 3: Formulation Chart

S. No.	Ingredient	F1	F2	F3	F4	F5	F6
1	Ofloxacin	100	100	100	100	100	100
2	HPMC K4M	50	100	125	-----	-----	-----
3	HPMC K15 M	-----	-----	-----	50	100	125
4	Sodium Bicarbonate	50	50	50	50	50	50
5	Magnesium stearate	3.5	3.5	3.5	3	3.5	3.5
6	Talc	3.5	3.5	3.5	3.5	3.5	3.5
7	Microcrystalline Cellulose	93	43	18	93	43	18
	Total weight	300	300	300	300	300	300

Table No. 4: Post Compression Parameters

S. No.	Formulation	Weight variation	Thickness (mm)	Hardness	Friability	Floating lag time	Floating Duration
1	F1	0.927 ± 0.05	3.0	4.5	0.38	1 min	< 30 min
2	F2	0.746 ± 0.02	3.5	5.0	0.43	2.5 min	>12 hrs
3	F3	0.835 ± 0.02	3.5	5.0	0.25	2.0 min	>12 hrs
4	F4	0.563 ± 0.08	3.5	5.00	0.27	1.5 min	>12 hrs
5	F5	0.563 ± 0.08	4.7	5	0.79	1.5 min	>12 hrs
6	F6	0.927 ± 0.05	2.1	2.5	0.31	2.0 min	>12 hrs

Table No. 5: Dissolution Profiles of Formulations

Sl. No	Time	% Cumulative Drug Release					
		F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	**0**
2	0.5	99.55	45.93	10.23	8.12	10.23	**4.13**
3	1	------	60.56	25.63	23.18	18.63	**10.25**
4	2	------	85.68	35.28	44.23	40.27	**18.12**
5	4	------	98.06	47.21	58.20	55.21	**40.95**
6	6	------	------	77.62	97.98	83.62	**63.54**
7	8	------	------	97.5	-------	98.59	**83.60**
8	10	-------	------	------	-------	-------	**94.33**
9	12	------	-------	-------	-------	-------	**99.65**

Dissolution release profiles of Formulations:

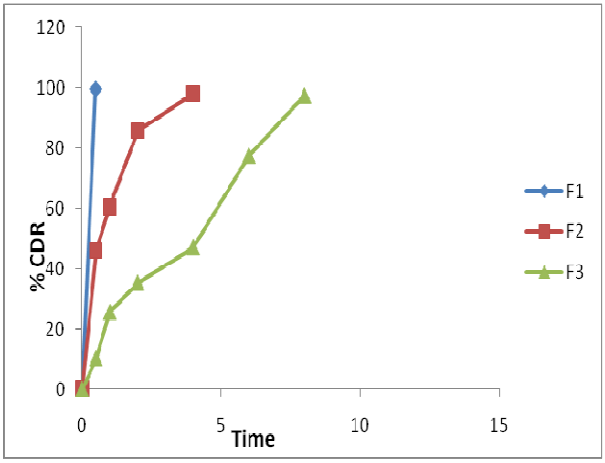


Fig. 2: % Cumulative Drug Release of F_1, F_2, F_3 Formulations

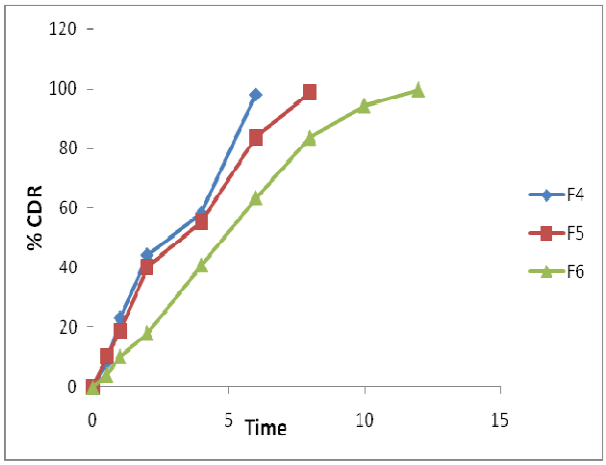


Fig. 3: % Cumulative Drug Release of F_4, F_5, F_6 Formulations

RESULTS AND DISCUSSION

F1 formulation floated instantaneously but it had no integrity, it got disintegrated into fragments as soon as it floated on to the surface F2 Formulation could prolong the drug release only till 4 hours of the study with the release of 98.06 and the dosage form lost its integrity at end of fourth hour.F3 formulation showed about 97.50% drug release at the end of 8hrs but the tablet lost its integrity and was broken down to fragments. F4 formulation had good integrity even till 6hrs of dissolution study but it the percentage drug release was 97.8 % at 6 hrs. F5 formulation had best integrity and could release maximum drug release by 10 hrs of dissolution study.F6 formulation high concentration polymer had best integrity and could sustain drug release till 12hrs of dissolution study Thus out of six formulations, F6 was promising for sustained drug release and formulation F6 was optimized based on % cumulative drug release at the end of 12 hours.

SUMMARY AND CONCLUSION

The formulations are evaluated for invitro dissolution studies, The formulation containing various ratios of HPMC 8.33%(F1) released almost 100%drug within 30min, where as incase of Ofloxacin tablet prepared with 16.66%(F2) released almost 100% drug within 4 hours, where as incase of Ofloxacin tablet prepared with 25%(F3) released almost 100% drug with in 8hours, where as incase of Ofloxacin tablet prepared with 33%, (F4) 6 hours & (F5) 10 hours, (F6) & released almost 100% drug within 12 hours. Thus out of six formulations, F6 was promising for sustained drug release and formulation F6 was optimized based on

% cumulative drug release at the end of 12 hours. UV spectrophotometric method was developed for the Ofloxacin. The method obeys Beer's law in the concentration of 2 - 10µg/ml with regression coefficient of 0.999. Thus the said method was found to be suitable for the estimation of Ofloxacin in invitro dissolution studies at λ max 277nm.

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