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FORMULATION DEVELOPMENT OF CR OFLAXACIN MATRIX TABLET AND THEIR *IN-VITRO* EVALUATION

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Abstract:

Among the all sophisticated drug deliveries oral drug delivery is known as safest and most convenient rout of administration. DDS are formulated for rapid release, for CDD (Controlled Drug delivery and release) and for targeted drug delivery. Controlled delivery system is the system which deliver the active ingredient at a predetermined rate and time for the local or systemic effect for a definite period of time. Formulation and development of CR made possible by the polymers i.e is synthetic polymers and natural polymers. Eudragit is an Synthetic amorphous polymer, which is non absorbable, non-biodegradable, and non-toxic polymers. Ofloxacin is a synthetic antibiotic of the fluoroquinolone drug considered to be a second generation flouroquinolone.(12) (13) ofloxacin is approved for the treatment of bacterial infection like chronic bronchitis, community acquired pneumonia, acute pelvic inflammatory disease complicated urinary tract infection. In this study CR drug formulated of Ofloxacin by adding Xanthan Gum and Eudragit RL100 polymers with direct compression method. Pre-formulation studies were conducted which all were according to the standards. Three different drug and polymers ratios were incorporated of two different polymers i.e. 10.3, 10.4, 10.5. Invitro dissolution studies were also conducted, the %age release was enhanced in all formulation. The formulation 10.3 in both formulations enhanced the release rate more than the other formulations. These polymers can also be used in other drug preparations and also suitable for development of CR formulations which may extended the drug release.

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INTRODUCTION:

Among the drug deliveries the most widely used drug delivery is oral drug delivery which is easily delivered, handled and less unwanted effects. Almost the oral rout can deliberated the most natural, suitable, nontoxic and safest due to easily administration, patient compliance and the less cost of manufacturing process. Pharma products which are designed for oral rout are mostly immediate released type or conventional type of drug delivery systems, which are formulated for rapid release of the drug for their rapid absorption (1, 2). These rapid release formulations have some limits such as the Drugs have short half-life which requires frequent administration, also increases chances of the missing of the dose for unaffordable patient and their compliance.

The DD is a process of drug administration or a drug compound to attain the needed therapeutic effect (3). DDS are formulated for rapid release, for CDD (Controlled Drug delivery and release) and for targeted drug delivery. Controlled delivery system is the system which deliver the active ingredient at a predetermined rate and time for the local or systemic effect for a definite period of time (4). The basic aim is to increase the drug therapy, to protect the degradation of drug and to improve the patient compliance (5). Formulation and development of CR made possible by the polymers i.e is synthetic polymers and natural polymers. Eudragit is a Synthetic amorphous polymer, which is non-absorbable, non-biodegradable, and non-toxic polymers (6). Eudragit RL100 is swell able and permeable polymer and xantane gum is a natural polymer (7). Both Polymer are suitable for formulation of matrix tablets. A natural polymer, Xanthane Gum is best retarders in CR formulation. As the property of Xanthane Gum is concern it is a hetropolysaccharide and biopolymer, which is produced by the fermentation from the bacteria (08). Ofloxacin is a synthetic antibiotic of the fluoroquinolone drug considered to be a second generation flouroquinolone.(12) (13) ofloxacin is approved for the treatment of bacterial infection like chronic bronchitis, community acquired pneumonia, acute pelvic inflammatory disease complicated urinary tract infection. Ofloxacin is effected against the aerobic gram-positive or gram negative bacteria (14).The elimination half-life of Ofloxacin is 4-5 hours.

2. MATERIAL AND METHODS:

2.1 Materials

2.1.1 Chemicals:

Different following analytical grade chemical were used.

No.	Material	Made in/by
1	Monobasic Potassium Phosphate	China
2	Ofloxacin	Zafa Pharmaceuticals Karachi
3	Eudragit RS 100	China
6	Xanthan Gum	China
9	Mg-Stearate	China
10	Starch	China

2.1.2 Instruments:

The following many apparatuses which were used in this research work of CR Ofloxacin development. All of these apparatuses were standardized before use;

No.	Instruments	Made in/by
1	Friabilator	Germany
2	Dissolution apparatus	Germany
3	Beakers, Test tubes and volumetric flask	Japan
4	PH-Meter	USA
5	Vernier Caliper	Germany
6	UV-Visible spectrophotometer	Japan
7	Syringes	Pakistan
8	Tableting machine	Germany
9	Electronic Balance	Japan
10	Hardness Tester	Germany

2.2: Preformulation studies

These studies were conducted as per prescribed procedures, these Preformulation tests which were included and were done

1. Solubility studies,
2. Standard curve,
3. Bulk density,
4. Compatibility study,
5. Hausner's ratio,
6. Tapped density, and
7. Angle of repose all these tests were done for the Ofloxacin (active drug).

2.2.1. Standard Curve of Ofloxacin

First of all phosphate buffer was prepared before construction of standard curve. 5 (diverse) dilutions were prepared from the stock solution accordingly as mentioned in the standards and then analyzed the absorbance spectrophotometrically.

2.2.2 Phosphate buffer solution

1.2 pH Phosphate buffer was made by adding 200 ml according to the standard procedures.

2.2.3. Stock solution Preparation

Prepared 100 ml of Ofloxacin stock solution by adding of 20 mg Ofloxacin in pH 1.2 phosphate buffer in a volumetric flask (100 ml) and volume was made 100ml up to the mark which contained 0.2mg per ml of active ingredient Ofloxacin.

2.2.4. Preparation Ofloxacin different dilutions

With the help of original stock solution 5 different dilutions were made by adding 50ml stock solution and added 50 ml buffer of 1.2 pH solution to make that solution up to the mark i.e. 100 ml and repeated this for five different dilutions making 100 ml solutions from every next dilution. First dilution contained 0.1mg per ml of Ofloxacin, second dilution contained 0.5mg per ml Ofloxacin, third dilution contained 0.25mg per ml Ofloxacin, forth dilution contained 0.0125mg per ml and the fifth dilution which contained 0.00625mg per ml.

2.2.5 Spectrophotometric analysis of stock solutions

These five different dilutions of Ofloxacin were further analyzed with the help of UV- Visible spectroscopy at 294 nm, the readings of absorbance were noted.

2.2.6. **Solubility studies of Ofloxacin**.

Solubility studies of Ofloxacin were performed by using distilled water with different temperatures at pH 1.2 for 24 hours. 100 mg of Ofloxacin was added in hundred ml solvent in a volumetric flask and kept in shaker. The shaker temperatures were kept accordingly according to the condition. Five ml sample were took and analyzed by spectrophotometer at 294 nm wavelength.

2.3: Preparation of CR Ofloxacin Tablets:

CR tablets contained Ofloxacin were developed by the method of direct compression and used variable concentrations of polymers, Mg stearate and filler were incorporated shown in table No 2.1 and 2.2.

All the ingredients were weight accurately and were passed through the sieve size no 60 mesh. Before, mixing uniformly all ingredients except Talc and Mg stearate were mixed togather with the help of mortar and pestle for fifteen minutes. After through mixing of active ingredient with the other excipient, 1% Talc & Mg stearate were added, as post lubricant. These all components were mixed again for 2- 3 minutes. The blended mixture was then compressed with the help of single tableting machine.

Table. 2.1 Designing of 100mg Ofloxacin Matrix CR tablet by adding the polymers (Xanthan Gum)

Drug and the Polymer Ratio	Ofloxacin	Polymers	(Mg St. 0.5%)	Starch
		Xanthan Gum		
10:3 (F1)	50 mg	15mg	0.5mg	34.5mg
10:4 (F2)	50 mg	20mg	0.5mg	29.5mg
10:5 (F3)	50 mg	25mg	0.5mg	24.5mg

Table No. 2.2 Designing of 100mg Ofloxacin Matrix CR tablet by adding the polymers (Eudragit RL 100)

Drug and the Polymer Ratio	Ofloxacin	Polymers	(Mg St. 0.5%)	Starch
		Eudragit RL 100		
10:3 (F4)	50 mg	15mg	0.5mg	34.5mg
10:4 (F5)	50 mg	20mg	0.5mg	29.5mg
10:5 (F6)	50 mg	25mg	0.5mg	24.5mg

2.4.. PHYSICOCHEMICAL PARAMETERS

2.4.1: Hardness of the formulation

To evaluate the hardness of the CR Ofloxacin hardness tester both manual and electronic were used to avoid any error of the compressed tablets and results were tabulated.

2.4.2: Friability

20 CR Ofloxacin tablets were selected and then weighed accurately after weighing those 20 tablets were placed in friabilator which was operated for 100 revolutions per minute for four minutes. After that tablets were weight again and the loss in weight were noted and tabulated.

2.4.3: Weight variation

For this test randomly 20 of the formulated CR tablets of Ofloxacin were selected and individually tablets were weighed to check any weight variation among these formulated tablets (15).

2.4.4: Drug content:

For determination of drug contents 5 tablets of CR Ofloxacin were grinded and powdered with the help of mortar & pestle. An exact weighed 100mg quantity of that powdered was extracted in 0.1N HCl at 1.2 buffer pH and that solution was filtered over 0.45µ filter membranes. Each of the tablet extracts were appropriately diluted and then theses were examined spectrophotometrically at 294 nm.

2.5: In-vitro dissolution evaluation

This study was carried out by using dissolution apparatus .In-vitro release studies were examined, each vessel was filled up to 900 ml of 0.N HCl the pH was maintained 1.2 and temperature was set on 37±0.5 ^{o}C ,the rotations were kept 50 per minute. At different time intervals 5ml samples were collected up to 24 hrs and as this 5ml were replaced with same pH solution. The %age release were noted and tabulated using statistical equations and interpreted (16).

2.6. DRUG RELEASE KINETICS

To investigate the mechanism of the CR Ofloxacin release rate kinetics, all the data obtained from these formulations developed were fitted into zero order, Higuchi model ,first order and Korsmeyer's equation release models (17,18).

3. RESULTS AND DISCUSSION:

Table No 3.1. Standard graph for the estimation of Ofloxacin

Concentration(µg/ml)	Absorbance (nm)
10	0.08
12	0.23
14	0.429
16	0.588
18	0.799
20	0.99

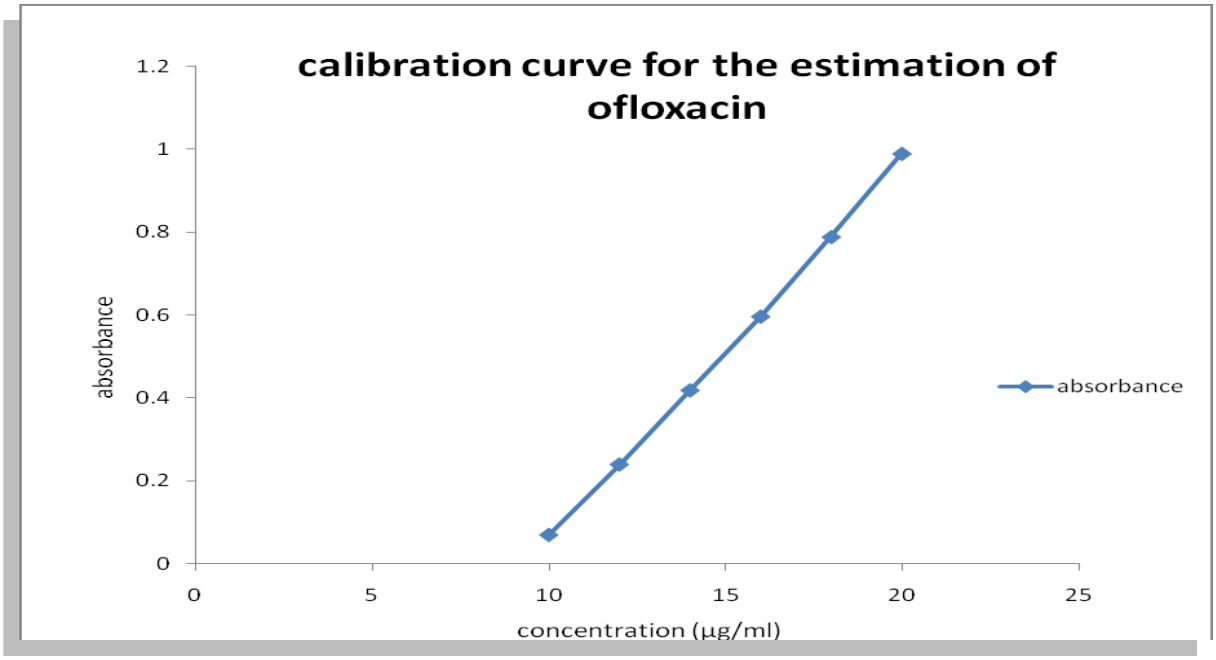

Figure 3.1. Calibration curve for the estimation of Ofloxacin

3.1. Pre-formulation Experiments

Results of the Angle of repose, compressibility and Hausner's ration were done for formulation F1 to F6 are shown in Table 3.2.

All values of angle of repose were found in this research work with in the acceptable limits ranged from 24º.96´ to 26º.43´. This shows that these powders flow properties were good and were accordingly. The results of the Compressibility index showed the limits raged in between 12.13% and 14.21% that indicated the powder has the necessary flow properties for tablet formulation as wet granulation. While the Hausner ratio also found within the limits which ranged between 1.110 to1.122.

Table 4.2: Pre-compression evaluation parameters

S.No	Angle of repose (θ)	Compressibility Index (%)	Hausner's ratio
F1	24.96±0.03	13.29±0.014	1.119
F2	25.39±0.05	12.13±0.020	1.110
F3	26.43±0.06	14.2110.023	1.122
F4	25.33±0.05	13.55±0.021	1.115
F5	26.13±0.05	12.95±0.124	1.131
F6	26.52±0.04	13.36±0.016	1.116

Table 3.3. Physical Characteristics of Ofloxacin CR Tablets

Formulation	Hardness Kg/cm2 (n=3) Mean±SD	Weight Variation (mg) (n=20) Mean±SD	Friability (%) (n=10)	Thickness (n=3)	Drug Content (%) (n=3) Mean±SD
F1	5.7±0.3	669±3.0	0.16	3.2±0.102	250.6±0.5
F2	5.6±0.2	678±3.0	0.14	3.4±0.112	249.8±0.3
F3	5.5±0.3	711±1.0	0.17	4.1±0.111	248.2±0.5
F4	5.6±0.2	677±2.0	0.17	4.0±0.105	250.0±0.2
F5	5.6±0.3	712±2.0	0.13	3.6±0.113	250.4±0.5
F6	5.9±0.1	711±1.0	0.15	4.2±0.108	251.9±0.2

All the formulations of Ofloxacin CR tablets were physically analyzed, their hardness, thickness, friability, weight variation and drug content and were matched with standard specifications. These CR Ofloxacin showed hardness in the limits and ranged from 5.5±0.3 to 5.9±0.1 kg/cm2 these results indicate that all the CR formulations of Ofloxacin were within the limits and having mechanical strength. Weight variations of the CR Ofloxacin formulations were within the limits specified in the Pharmacopeia and ranged from 69±3.0 to 712±2.0. The friability tests of these formulation done and the results were within the limits and ranged from 0.13 to 0.17% these results of friability shows that all the tablets values were below the recommended standards i.e. 1%. So this result show resistance from any mechanical abrasion and shock and also indicates good compatibility of the tablets. The thicknesses of those formulations were checked accordingly and it showed that the tablets are within the limits ranged from 3.2±0.102 to 4.2±0.108mm. The %age contents of those formulations were showed within the limits it ranged from 248.2±0.5 to 251.9±0.2 %.(table No 3.3).

Table 3.4. Drug Release Profile of CR Ofloxacin Matrix Tablets

	Time (hrs)		0	1	2	4	6	8	10	12	16	20	24
Cumulative % Drug Released		**F1**	0	3.23	17.22	29.11	40.01	48.12	53.23	63.48	72.87	85.11	97.01
		F2	0	5.34	21.22	33.51	42.13	52.20	59.17	69.01	78.05	88.89	94.62
		F3	0	12.22	23.17	36.10	44.15	50.11	58.23	68.22	73.09	82.22	92.02
		F4	0	10.31	24.52	41.12	48.56	56.22	63.56	73.00	82.23	87.25	98.20
		F5	0	13.10	19.06	31.02	36.51	42.23	56.20	61.20	73.25	81.20	92.20
		F6	0	9.23	23.00	32.02	39.23	43.25	53.22	62.25	74.32	81.52	91.02

In-vitro Dissolution Studies:

Dissolution *In-vitro* studies of all C R Ofloxacin formulations were performed in 0.1 N HCl. The dissolution studies and the study was performed for 24 hrs, and the accumulative drug percentage releases were noted at different time intervals after that the results of dissolution were tabulated of each of the formulation F1 to F6 (Shown in table 4.4). The drug release % age verses Time in hours for all formulations (F1 to F3) were shown in Figure No 4. 2 and formulation (F4 to F6) were shown in figure No 4.3. As the quantity of the polymers increases the % age release of the drug indicated decrease. As the amount of polymer quantity is less with drug combination the %age release showed increase in %age. Two different polymers were used in different ratios Ofloxacin with polymer Xanthan Gum used as (F1 to F3) 10:3, 10:4 and 10:5, subsequently Ofloxacin with polymer Eudragit RL 100 (F4 to F6) with same ratio as in Xanthan Gum. In formulation F1 the ratio of drug and polymer was 10.3 which showed increased drug release 97.10%, as in formulation F2 and F3 where polymer ratio increased 10.4 and 10.5 and the %age release of drug were 94.32% and 92.02% in 24 hours. Where the same drug and polymer ratio were incorporated as Ofloxacin and polymer Eudragit RL 100 in formulations F4, F5, and F6, as 10.3, 10.4, and 10.5 it also gave good results in 10.3 formulation 98.20% as compare to the F5 and F6 92.20 and 91.02%. These results of all formulations confirms that all formulations were anomalous non fickian mechanism but both formulations of Ofloxacin with Xanthan Gum and Eudragit RL100 polymers at 10:3 releases the drug by non fickian diffusion or it showed near to zero-order release kinetics. It was also observed and confirmed that Eudragit RL100 is by nature a hydrophobic polymer and it may retarded the medium of dissolution by penetrating into the matrices which exhibited in prolonged the drug release profile and it also indicated which increased the molecular volume of these hydrated polymer with a decreased in free space as microspore are existing (Kan and Zhu, 1999, Rehman et al., 2013).

CONCLUSION:

The conclusion of this study work is that the polymers used Xanthan Gum and Eudragit RL100 both were showed extended results up to 24 hours. All these Ofloxacin CR formulations indicated that when Ofloxacin drug is combined with polymer the decrease in polymer ratio increases the drug release where the polymer ratio increases it decreases the drug release and these results showed that in F1 and F4 where the drug and polymer ratio were 10.3 increased the drug release in both polymers. These polymers can also be used in other drug preparations and also suitable for development of CR formulations which may give results and extended the drug release. In these CR formulation developments it improves the patient compliance and also cost of these formulation will be very low.

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