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Formulation and evaluation of rapid disintegration tablets of moxifloxacin HCl

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ABSTRACT

The poor aqueous solubility of the drug results in variable dissolution profile and hence poor bioavailability. The aim of present work was to show the effect of various super disintegrants on the disintegration time and in vitro drug release rate. In this study, an attempt has been made to prepare rapid disintegrating tablets of the drug using different super disintegrants following wet granulation method. The Tablets were formulated by wet granulation method, using Mannitol as diluent. Crospovidone (XL-PVP) (6 and 8%), croscarmellose sodium (Ac-Di-Sol®) (6 and 8%), Sodium starch glycolate (6and8%) were used as super disintegrants at different concentrations. The Precompression parameters like bulk density, tapped density, Carr's Index and angle of repose were determined. The post compression parameters like the hardness, thickness, friability, weight variation, Disintegration time, in-vitro dissolution, FT-IR studies were carried out to check whether any interaction had occurred, results were promising. HPLC method was used to find out the percentage drug content and was found to be 99.6%.The optimized formulation was selected based on the results and stability studies were carried out on the optimized formulation and the percentage drug release was found to be 97.8%.

Keywords: Rapid Disintegration; Moxifloxacin Hydrochloride; Compression; Hardness; Microcrystalline cellulose.

INTRODUCTION

Geriatric patients may have difficulty in swallowing and chewing the tablets resulting in patient non compliance and ineffective therapy. To overcome these problems rapid disintegrating tablets (RDT) are good option. Since, they disintegrate and dissolve rapidly in saliva without need for drinking water. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Rapid disintegrating tablets are also useful in patients [5, 6] like pediatric, bedridden, or mentally disabled, who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy. [7, 8] Such problems can be resolved by means of rapid disintegrating tablets. Conventional tablet and hard gelatin capsule dosage forms possess higher disintegration time so patients obtain pharmacological effect after 30 to 45 minutes of dosage form administration [11]. This RDT disintegrates instantaneously when placed on tongue and releases the drug dissolves or disperses in the saliva [4]. This can be achieved by addition of various superdisintegrants like croscarmellose sodium, crospovidone, sodium starch glycolate alone or in various combinations which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva[1-3].

Moxifloxacin is a fourth-generation synthetic fluoroquinolone antibacterial agent. It is used for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, complicated and uncomplicated skin and skin structure infections, and complicated intra-abdominal infections [13]. Moxifloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication. The half-life of moxifloxacin is 11.5-15.6 hours. The present invention deals with the development of effective and stable rapid disintegrating tablets of moxifloxacine having adequate hardness, low disintegration time and pleasant taste [14]. Its poor solubility in water and bland taste makes it an ideal candidate for fast dissolving tablet with regards to palatability. This leads to an increase in bioavailability by avoiding first pass metabolism [10]

Various techniques can be used to formulate orally disintegrating tablets or fast dissolving tablets. [6] wet granulation is one of the techniques requires the incorporation of a superdisintegrants into the formulation. The aim of purpose work was to formulate and characterization orally disintegrating tablets of moxifloxacine for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of bacterial infections.

MATERIALS AND METHODS

Moxifloxacin Hydrochloride, Sodium starch glycolate, Crospovidone, Croscarmellose sodium are obtained from the M/s Bright labs–Dilshuknagar, Hyderabad, Andhra Pradesh, India. Mannitol, Magnesium stearate, Aspartame is obtained from the richer pharmaceuticals, Hyderabad. All the chemicals and reagents used in the formulation were of analytical grade.

PREPARATION:
Moxifloxacin HCl tablets were prepared by wet granulation method.

Procedure of Wet Granulation:
Step 1: Weighing and Blending - the active ingredient, disintegration agents are Weighed and mixed.
Step 2: The wet granulate is prepared by adding the liquid binder/adhesive. The liquid solution can be either aqueous based or solvent based. In this formulation the binding solution is corn starch soution5%w/v is made.
Step 3: Screening the damp mass into granules.
Step 4: Drying the granules (in hot air oven at 60^0c for one hour).
Step 5: Dry screening: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity.
Step 6: Lubrication- A dry lubricant, gliding is added to the granules either by dusting over the spread-out granules or by blending with the granules. It reduces the friction between the tablet and the walls of the die cavity
Step 7: Tableting: Last step in which the tablet is fed into the die cavity and then compressed between a lower and an upper punch. 12mm size punches were used for punching tablets.

Six possible combinations of the Moxifloxacin hydrochloride RDT were prepared by varying proportions of the super disintegrants. The formulation and proportions of the various ingredients are shown in the table 1.

Master Formulation for Moxifloxacin Hydro Chloride:

Table 1: Master formulation

Ingredients	F1	F2	F3	F4	F5	F6
Moxifloxacin Hydrochloride	400mg	400mg	400mg	400mg	400mg	400mg
Crosspovidone	30mg	40mg	------	-------	-----	---------
Sodium Starch Glycolate	----------	……	30mg	40mg	-----	---------
Croscarmellose Sodium	----------	…….	-------	-------	30mg	40mg
Mannitol	145mg	135mg	145mg	135mg	145mg	135mg
Magnesium Sterate	15mg	15mg	15mg	15mg	15mg	15mg
Talc	5mg	5mg	5mg	5mg	5mg	5mg
Aspartame	5mg	5mg	5mg	5mg	5mg	5mg
TOTAL	**600mg**	**600mg**	**600mg**	**600mg**	**600mg**	**600mg**

Standard Graph Calibration Curve of Moxifloxacin Hydrochloride.
The UV scanning of drug sample was carried out using a solution of drug dissolved in 0.1N HCL solution at concentration of 100 µg/ ml. The $\lambda_{max\ was}$ observed at 293nm.

The calibration curve of Moxifloxacin hydrochloride was obtained by dissolving the drug in 0.1 N HCL solutions and absorbance was measured at 288nm in 0.1 N HCL solution used as blank. Beer's law was obeyed the concentration range of 1-9 µg in 0.1 N HCL solution.

PROCEDURE:
Accurately weighed quantity of Moxifloxacin Hydrochloride (100mg) was dissolved in 0.1N Hydrochloric acid and the volume made up to 100ml with the same.

S.S I ⇒ 1000 mcg/ml.

10ml of Stock solution I was further diluted with 100ml of pH 1.2 buffer to get a working standard **S.S I ⇒ 100mcg/ml** Aliquots of 1.0, 2.0,3.0,4.0,5.0,6.0,7.0,8.0 and 9.0 of stock solution was pipetted into 10ml volumetric flask and diluted up to the volume with 0.1N Hydrochloric acid. The absorbance was measured at 288nm against reagent blank (0.1N Hydrochloric acid).As shown in the figure 1 and table 2. Same procedure was employed to extract the standard graph for phosphate buffer 6.8. As shown in the figure 2 and table 3.

Table: 2 Standard Graph Results Of 0.1n Hcl

Concentration (µg/Ml)	Absorbance At 288nm
1	0.113
2	0.216
3	0.334
4	0.441
5	0.557
6	0.67
7	0.75
8	0.878
9	0.976

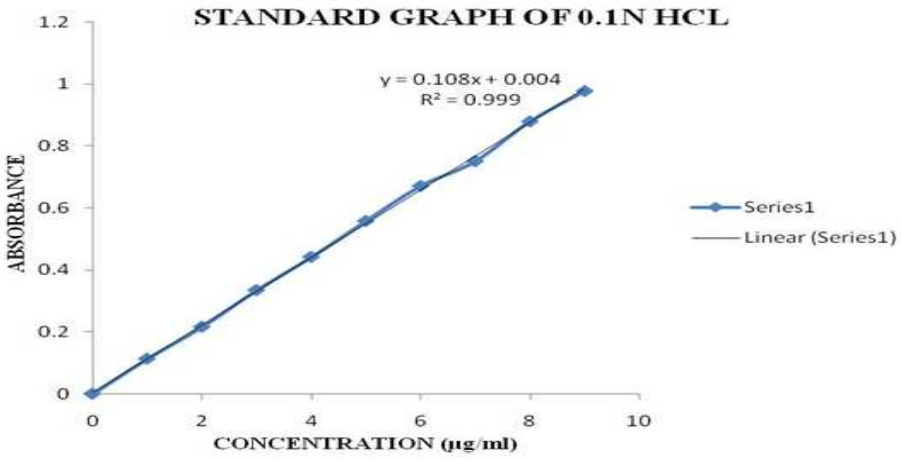

Fig: 1

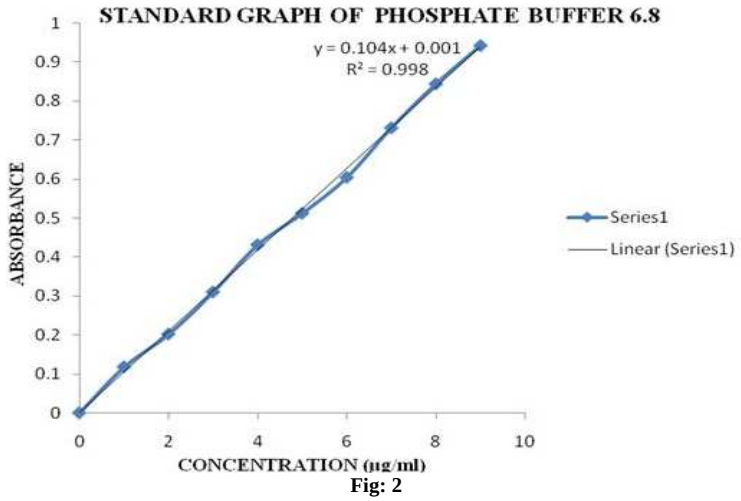

Fig: 2

Table: 3 Standard Graph Results With Phosphate Buffer 6.8

Concentration (µg/Ml)	Absorbance At 288nm
1	0.118
2	0.202
3	0.31
4	0.431
5	0.512
6	0.604
7	0.731
8	0.844
9	0.942

COMPATIBILITY STUDY:

The pure drug and prepared floating tablet were subjected to IR spectroscopic study using FT-IR spectrophotometer (IRAffinity-1, Shimadzu). The spectra were scanned over the wave number range from 4000^{-1} – $400cm^{-1}$. The pellet press techniques were used for sample testing's.

EVALUATION PARAMETERS:

Pre-compression Parameters:

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 weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder

Tapped Density (D_T):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$D_T = \frac{M}{V_1}$$

Where, M is the mass of powder, V_T is the tapped volume of the powder

Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of Repose:
The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

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. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Carr's Index (I):
It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by table 4

$$I = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

Table: 4 Carr's Index limit

Carr's index (%)	Type of flow
5 – 15	Excellent
12 – 18	Good
18 – 23	Fair to passable
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

Post compression Parameters:
Hardness:
The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in Kg / cm^2.

Friability (F):
The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (**%)**. 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated.

Weight Variation:
Ten tablets were selected randomly from the lot and weighed individually to check for weight variation.

Thickness:
The thickness of the tablets was measured by screw gauge. It is expressed in mm**.**

Disintegration Time:
The *Invitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Content uniformity test:
Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of formulation was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stopper flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The drug content was determined by measuring the absorbance at 288 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated.

Invitro dissolution studies:
The *Invitro* dissolution study was carried out in USP dissolution test apparatus type 2 (paddle). With Dissolution Medium as 900ml of simulated gastric fluid at a Temperature: 37 ± 0.5 ^{o} C with RPM: 50. Volume withdrawn & replaced: 5 ml every five minutes and analyzed using UV detection at a wavelength of 288nm. Dissolution profile was compared with innovator tablets with the help of similarity factor (i2) calculation [19].

Wetting time:
Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The time required for water to reach upper surface of the tablet is noted as a wetting time. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured. The method was slightly modified by maintaining water at 37^{o} c. A tablet was placed on the tissue paper and small amount of amaranth powder was placed on upper surface of tablet. The time required for development of a red color on the upper surface of the tablet was recorded as wetting time.

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, Wa is weight of tablet before water absorption
Wb is weight of tablet after water absorption
R is water absorption ratio.

Stability studies:
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

Long-Term Testing: 25 ^{0} C ± 2 ^{0} C / 60% RH ± 5% for 12 Months
Accelerated Testing: 40 ^{0} C ± 2 ^{0} C / 75% RH ± 5% for 6 Months

Method
The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40 ^{0} C / 75% RH for 3months and evaluated for their physical appearance, drug content and drug excipient compatibility at specified intervals of time (table:5 fig:8).

Table: 5 Stability Data of Formulation 6 at 40 ± 2^{0}C / 75 ± 5% RH

Sl. No.	Time in days	Physical changes	Percentage of drug content* ±SD	Moisture content	Percentage of drug release * ±SD (99.5% of release label claim in 10 min).
1.	1st day (initial)	Round, yellow color uncoated tablets with plain on both side.	99.51±0.48	0.82	99.5%
2.	30th day (1 month)	No changes	99.35±0.11	0.78	99.2%
3.	60th day (2 month)	No changes	98.12±0.13	0.80	99.3%
4.	90th day (3 month)	No changes	97.81±0.28	0.78	99.2%

** SD- Standard deviation*

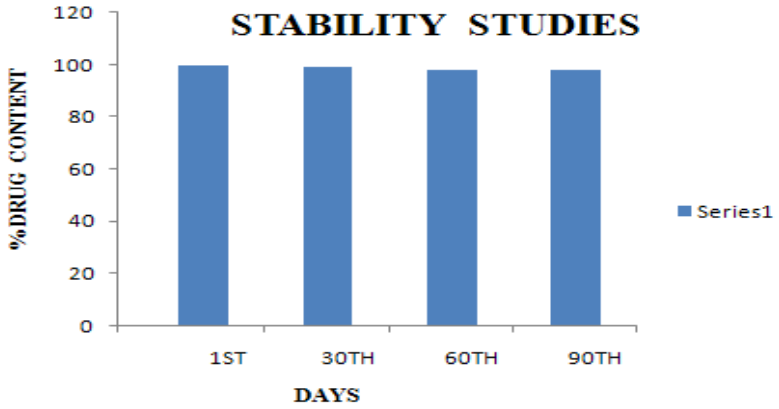

Figure: 8 Graphs Showing %Drug Content.

RESULTS AND DISCUSSION

FT-IR study:

Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between moxifloxacine hydrochloride and the polymers used. Drug has given peaks due to furan ring, secondary diamine, alkene and two peaks due to nitro functional groups. Form the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. (fig: 3, 4, 5, 6, 7)

Pre-compression parameters:

Precompression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. The two most important attributes for the direct compression formula are good flow and good compressibility. Interparticulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder such a comparison often used as an index of the ability of the powder to flow. The angle of repose gives important information about the flow characteristics of the powder mixture. The powder flow depends on three general areas: The physical properties of the particle (e.g., shape, size, compressibility), the bulk powder properties (e.g., size distribution, compaction), and the processing environment (e.g., storage, humidity table 6)

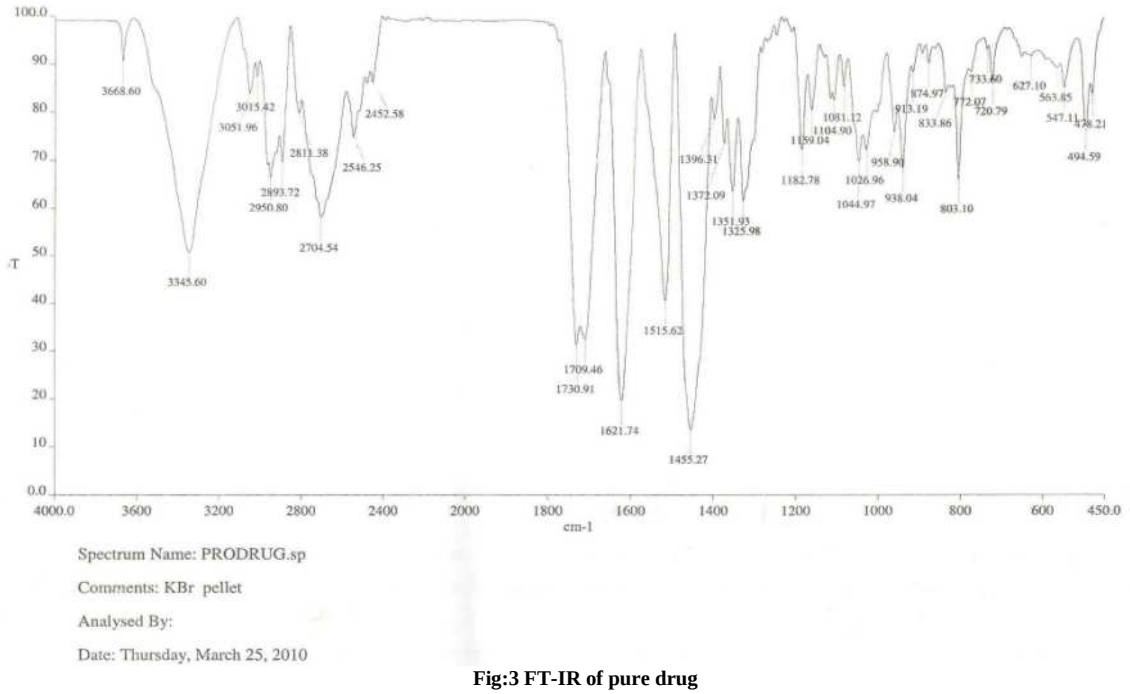

Fig:3 FT-IR of pure drug

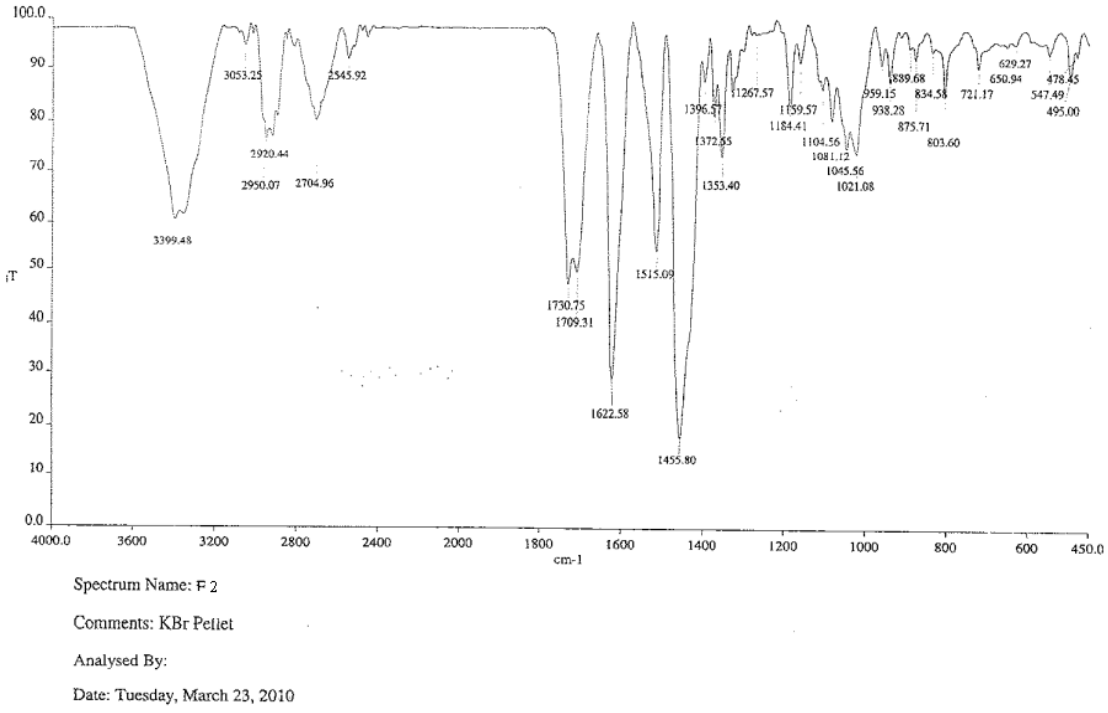

Fig: 4 FT-IR of croscarmellose sodium

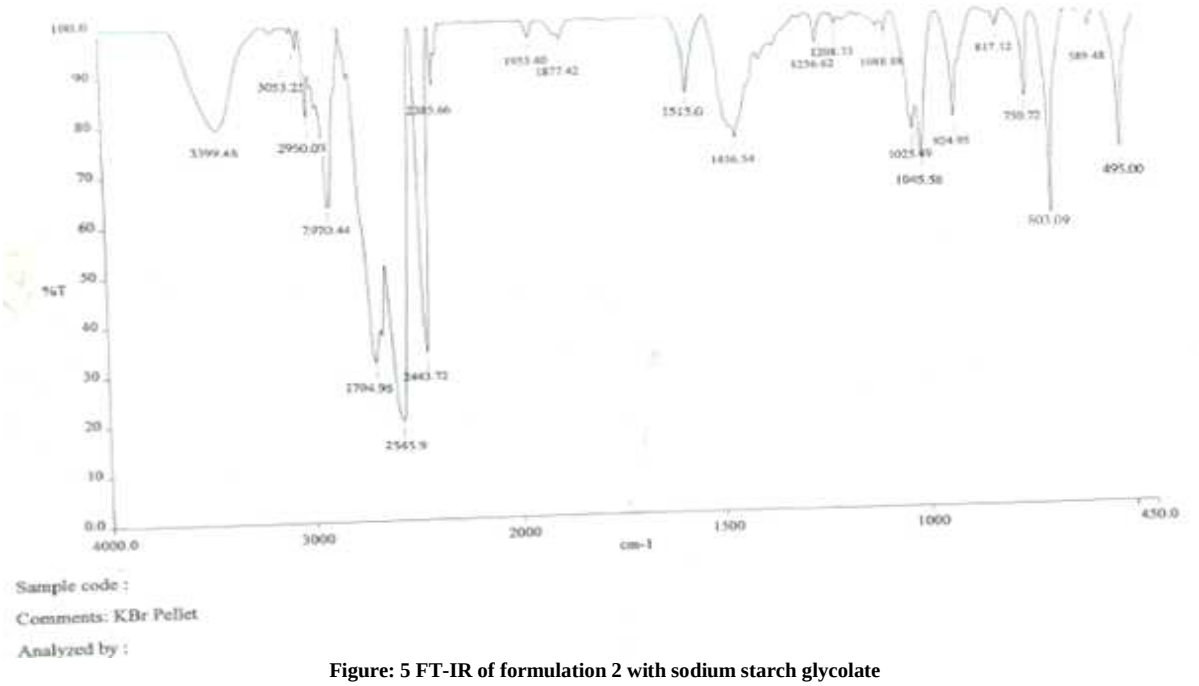

Figure: 5 FT-IR of formulation 2 with sodium starch glycolate

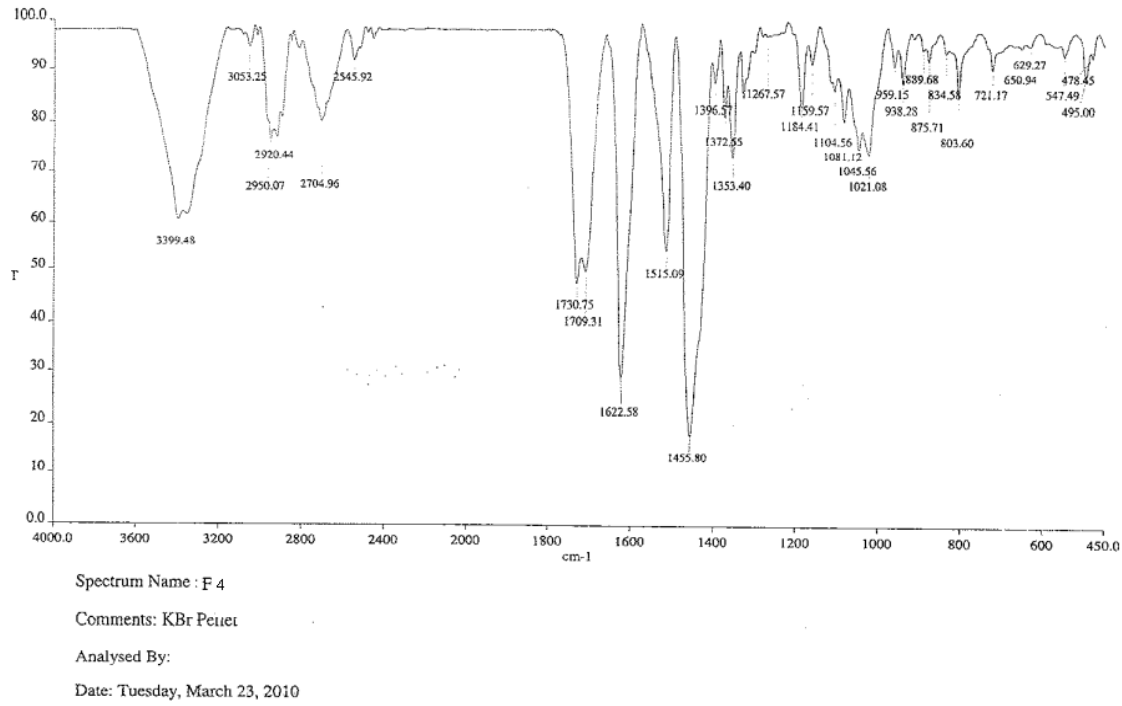

Figure: 6 FT-IR of formulation 4 with crospovidone

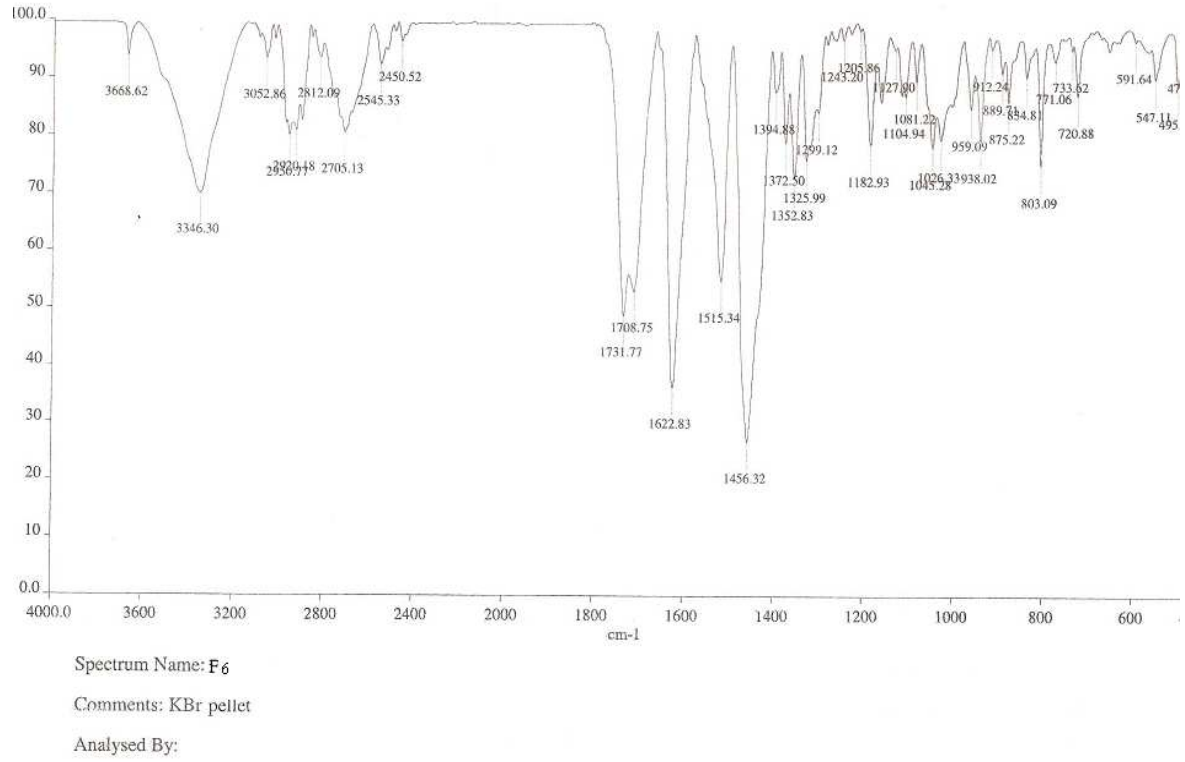

Figure: 7 FT-IR of formulation 6 with croscarmellose sodium

Table: 6 Pre-compression parameters of Moxifloxacin Hydrochloride

Formulation number	Bulk Density	Tapped Density	Carr's Index	Hausner ratio	Angle of repose
F1	0.52± 0.36	0.65± 0.44	20.02± 0.32	1.21± 0.33	34.2± 0.31
F2	0.55± 0.48	0.64± 0.32	26.21± 0.36	1.16± 0.38	35.5± 0.42
F3	0.49± 0.22	0.57± 0.18	14.04± 0.16	1.18± 0.12	33.2± 0.20
F4	0.48± 0.11	0.55± 0.20	12.72± 0.15	1.14± 0.14	32.4± 0.14
F5	0.50± 0.18	0.58± 0.16	13.79± 0.17	1.16± 0.15	33.0± 0.12
F6	0.53± 0.21	0.61± 0.11	13.11± 0.15	1.15± 0.12	32.1± 0.22

Post compression parameters:

The hardness of the tablets was found to be 4.4 ±0.03 to 4.8± 0.057 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 3.8± 0.057 to 3.9± 0.04. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopeial limits i.e. ±7.5%. The drug content was found to be 98.02 to 99.89%, indicating uniform distribution of drug in the tablets. Wetting time for the various formulations is given in the table 7.

Table: 7 Post compression parameters of Moxifloxacin Hydrochloride

PARAMETERS	F1	F2	F3	F4	F5	F6
Hardness (Kg / cm^2)	4.6± 0.02	4.8±0.05	4.7± 0.06	4.8± 0.04	4.5± 0.03	4.7± 0.02
Friability (%)	0.62±0.011	0.64±0.016	0.76±0.008	0.89±0.006	0.64±0.012	0.46±0.008
Thickness (mm)	3.8± 0.02	3.6± 0.08	3.9± 0.06	3.8± 0.04	3.8± 0.03	3.8± 0.02
Disintegration time (sec)	122 ± 1.03	116 ± 1.27	96 ± 1.25	82 ± 1.16	54 ± 1.06	40 ± 1.02
Weight variation(average weight)(mg)	602.4 ± 0.12	602.6 ± 0.19	602.2 ± 0.05	602.4 ± 0.04	602.6 ±0.07	602.2 ± 0.01
Wetting time(sec)	214.00 ± 0.95	175.00 ± 0.84	57.00 ± 1.04	49.00 ± 0.53	46.00 ± 0.65	35.00 ± 1.48
Content uniformity	98.98±0.81	98.73±0.61	99.41±1.21	99.50±0.32	99.92±0.11	99.97±0.61

** SD- Standard deviation*

DISCUSSION

Six formulations of Moxifloxacin HCl were prepared with varying concentrations of three superdisintegrants: crospovidone, crosscarmellose sodium, sodium starch glycolate, were used. (Table1). For each formulation, blend of drug and excipients were prepared by wet granulation method and evaluated for various parameters as specified earlier. The powder blend was compressed using direct compression technique. Bulk density was found in the range of 0.48-0.55 g/cm^3 and the tapped density between 0.55-0.65 g/cm^3 and Angle of repose between 35.1-35.2. Using these two density data Hausner's ratio and compressibility index were calculated. The powder blends of all formulations had Hausner's ratio less than 1.25 indicating better flow properties. The compressibility index was found between 8.88- 14.8, which indicates good flow ability of the powder blend values are given in table 6. The good flow ability of the powder blend was also evidenced with angle of repose (range of 26-30) which is below 40^o indicating good flow ability. Tablets were prepared using direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per I.P. The drug content was found in the range of 98.02%m-99.89% (acceptable limit) and the hardness of the tablets were found below 4.6 kg/cm^2 and friability were found 0.63-0.86 indicating a good mechanical resistance of the tablets, and the parameters were found well within the specified limit for RDT tablets. The *in-vitro* disintegration time (DT) of the tablets was found to be less than 3min, wetting time 21-61 sec ,water absorption ratio 34-64sec, the percentage drug release was found to be 99.29% in a 10 mints fig 9 and 10 (table: 8, 9). The order of enhancement of the dissolution rate with various superdisintegrants was found to be: crospovidone> crosscarmellose> sodium starch glycolate. The preparation process in direct compression tablets includes co- grinding of all the excipients before compression, results in increase in solubility due to the reduction in the effective particle size of the drug following increase in the wetting of drug particle by the excipients and improved dissolution of drugs. It was concluded that fast disintegrating tablets of Moxifloxacin HCl can be successfully prepared with selected superdisintegrants in order to improve disintegration/dissolution of the drug in oral cavity and hence better patient's compliance leading to effective therapy.

Dissolution Studies

Table: 8 Dissolution tables of formulations in 0.1N HCL

Time	F1	F2	F3	F4	F5	F6
5min	88.6±0.25%	90.3±0.26%	89.8±0.29%	92.6±0.19%	91.7±0.37%	92.6±0.51%
10min	92.6±0.55%	99.2±0.17%	94.8±0.33%	99.3±0.28%	99.6±0.45%	99.5±0.49%
15min	99.6±0.43%		99.2±0.41%			

** SD- Standard deviation*

Table: 9 Dissolution Table of Formulations in phosphate buffer 6.8

Time	F1	F2	F3	F4	F5	F6
5min	89.9±0.15%	91.6±0.25%	88.8±0.65%	90.18±0.33%	92.4±0.39%	95.6±0.52%
10min	94.6±0.61%	96.2±0.36%	93.2±0.66%	96.42±0.50%	96.8±0.70%	99.51±0.48%
15min	97.1±0.53%	99.45±0.45%	96.25±0.56%	99.22±0.45%	99.2±0.67%	
20min	99.4±0.72		99.11±0.29%			

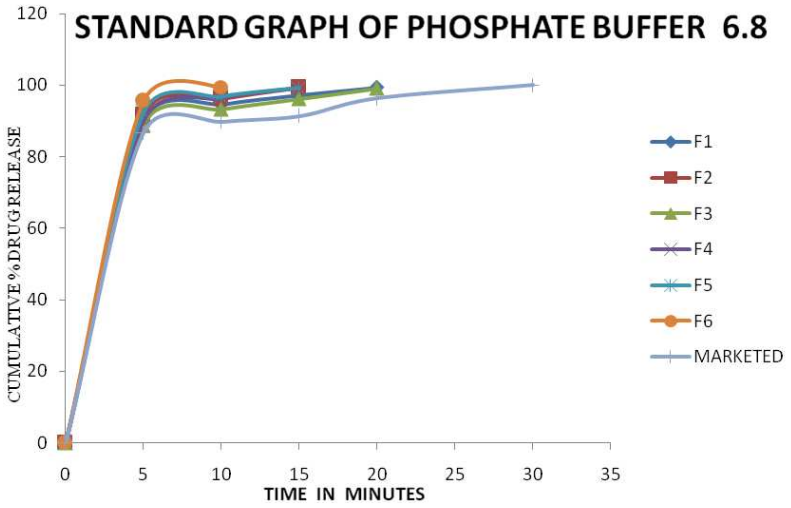

Figure: 9 *In-vitro* release data in phosphate buffer 6.8

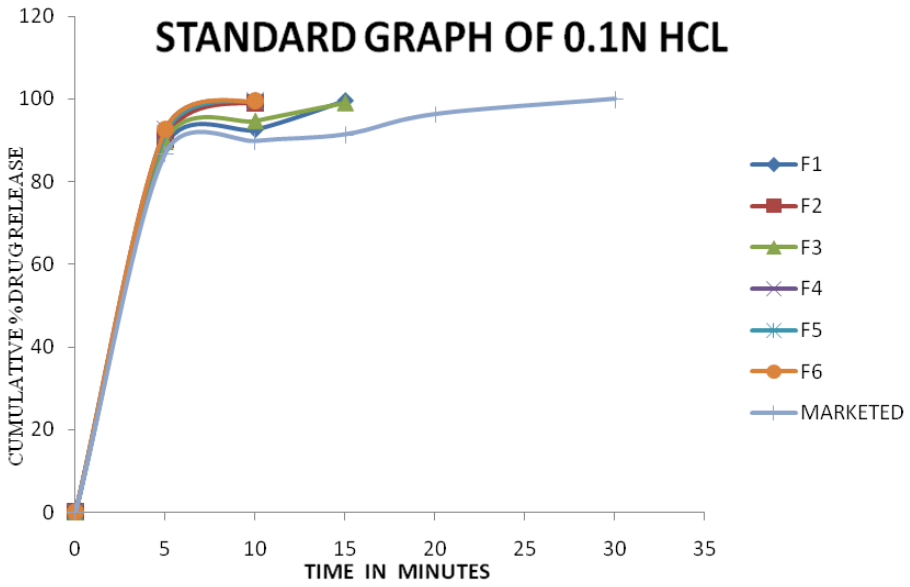

Figure: 10 *In-vitro* release data in 0.1N HCl

COCLUSION

Rapid disintegrating tablets of Moxifloxacin hydrochloride were prepared by wet granulation method using crospovidone, Sodium starch glycolate and croscarmellose sodium as superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. In vitro drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrants based rapid disintegrating tablets of Moxifloxacin hydrochloride would be quite effective in providing quick onset of action without need for water for swallowing or administration.

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