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Research article

DESIGN AND DEVELOPMENT OF LEVOFLOXACIN HEMIHYDRATE FAST DISSOLVING TABLETS USING FENUGREEK POWDER

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ABSTRACT: Levofloxacin hemihydrate is an antibiotic used for bacterial infections. It belongs to flouroquinolones class. Fast dissolving tablets gaining popularity over conventional tablets due to their convenience in administration and suitability for patients like geriatrics and pediatric patients because of their swallowing difficulties. The half-life of the drug is 6-8 hrs and it is rapidly and completely absorbed after oral use for that levofloxacin prepared as fast dissolving tablets. Tablets were prepared by direct compression technique by using MCC as binder. Super disintegrants used are SSG(2%,3%,4% and 5%),CCS(AC-DI-SOL) (2%,3%,4%and 5%), CP(2%,3%,4%and5%)and FGP(2%,3%,4%and 5%),.Among these 4 super disintegrants, Fenugreek powder (FGP) was show best results in the evaluation tests.

Key words: Fast dissolving tablets, Levofloxacin hemihydrate, direct compression technique, super disintegrants.

INTRODUCTION

Mouth dissolving/disintegrating tablets (MDTs) or fast dissolving tablets are novel types of tablets that dissolve/disintegrate/ disperse in saliva within few seconds without water. (Sastry S, Nyshadham J, 2000) According to European pharmacopoeia, these MDTs should dissolve/disintegrate in less than three minutes. Other names of fast dissolving tablets (FDT'S) are orodisperse, mouth-dissolving, quick dissolve, fast-melt, mouth-melt tablets. (Reddy L, 2002) The formulation is more useful for the bed-ridden and patients who have the swallowing problem.

Dysphasia, or difficulty in swallowing, is most common problem in old age people. The main reasons for difficulty in swallowing tablets size, surface, form and taste of the tablets. These types of fast dissolving tablets are mostly useful for geriatric and pediatric patients and travelling patients who may not have ready access of water. The disintegration time for good FDTs varies from several seconds to about a minute (Yourong Fu, Schicheng Yang, 2004) . FDT's have been found to be the choice for psychiatric, patients suffering from stroke, thyroid disorder, Parkinson's disease, multiple sclerosis, patients with nausea, vomiting and motion sickness.(Kothawadae D, Wagh.M, 2010, Kuchekar B, Bhise S, 2001, Shukla D, Chakraborty S, 2009, Harada T, Narazaki R, 2006, Gohel.M,Pariksh R, 2007) To formulate FDT's by direct compression technique, it mostly suited for the drugs undergoing high first pass metabolism and is improving bioavailability with reducing dosing frequency to minimize side effects. (Zhao N, Aughsburger L, 2005) Direct compression does not require water or heat during the formulation and is the ideal method for moisture and heat labile drugs (Priya V,Rao G, 2009).

MATERIALS AND METHODS:

Levofloxacin hemihydrate was obtained as a gift sample from HETERO LABS LTD., Hyderabad. Sodium starch glycolate (SSG), Crospovidone (CP), Crosscaramellosesodium (CCS) were obtained from National Pharmaceutical Excipients and Chemicals, Guntur. Fenugreek powder (FGP), MCC, Magnesium stearate and Talc used were of analytical grade. The method used for formulation of fast disintegrating tablets of levofloxacin was direct compression technique.

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Direct Compression Technique:

This method is used when the ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be pre-processed. This requires the active ingredient to have appropriate physical and chemical properties, such as good compatibility and low stickiness. Direct compression is often preferred because of its simplicity and relatively low cost, but may not always be technically feasible.

In this method, all the powder excipients are mixed thoroughly in a polyethylene bag. After proper mixing, the powder was punched into tablets. The weight of the tablet was 370mg and dose of the drug is 250mg.

PREPARATION OF FENUGREEK POWDER:

It was a natural superdisintegrant and it is scientifically known as "***Trigonella fenugraceum***" commonly known as "fenugreek" is an herbaceous plant of *leguminaceae.*

It is one of the oldest cultivated plants and has found wide applications as a food additive and as a traditional medicine in every region. Fenugreek seeds contain a high percentage of mucilage which can be used as disintegrant for use in mouth dissolving tablets. Mucilage is off-white cream yellow colored amorphous powder that quickly dissolves in warm water to form viscous colloidal solution. The seeds are dried under sun light for removing moisture after that they are grinded in a mixer and the powder was sieved with sieve no:#40.

The powder sealed in a box and used as a superdisintegrant in the formulations.

Table 1: Batch Formulae of F1 –F10 Prepared by using synthetic super disintegrants

S.no	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Levofloxacin	250	250	250	250	250	250	250	250	250	250
2	Microcrystalline cellulose(MCC)	108.6	104.9	101.2	97.5	108.6	104.9	101.2	97.5	108.6	104.9
3	Sodium starch glycolate(SSG)	7.4	11.1	14.8	18.5	--	--	--	--	--	--
4	Crosscarmellose sodium	--	--	--	--	7.4	11.1	14.8	18.5	--	--
5	Crospovidone(CP)	--	--	--	--	--	--	--	--	7.4	11.1
6	Talc	2	2	2	2	2	2	2	2	2	2
7	Magnesium stearate	2	2	2	2	2	2	2	2	2	2
	Total weight	370mg									

Table 2: Batch Formulae of F11 and F12 Prepared by synthetic super disintegrant, F13-F16 prepared by natural super disintegrant.

Sno	Ingredients	F11	F12	F13	F14	F15	F16
1	Levofloxacin	250	250	250	250	250	250
2	Microcrystalline cellulose(MCC)	101.2	97.5	108.6	104.9	101.2	97.5
3	Crospovidone (CP)	14.8	18.5	--	--	--	--
4	Fenugreek powder(FGP)	--	--	7.4	11.1	14.8	18.5
5	Talc	2	2	2	2	2	2
6	Magnesium stearate	2	2	2	2	2	2

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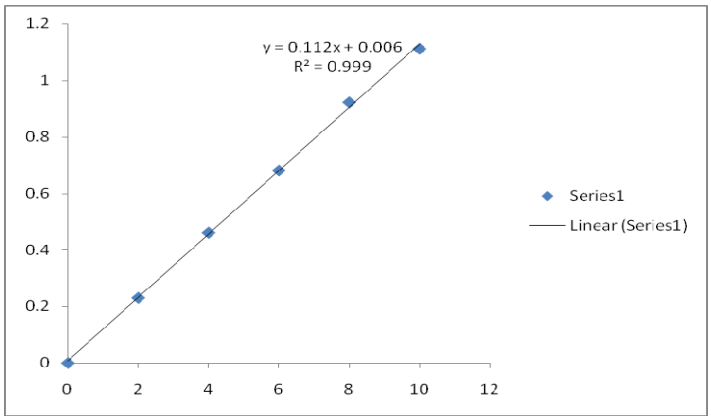
Table 3: calibration curve data of levofloxacin hemihydrates:

S.no	Concentration(µg/ml)	Absorbance(nm)
1	0	0
2	2	0.230
3	4	0.461
4	6	0.681
5	8	0.922
6	10	1.112



Graph 1: Calibration curve of Levofloxacin

Calibration curve procedure of levofloxacin pure drug:

50 mg of pure drug of levofloxacin was dissolved in 50ml volumetric flask. The drug was shaked with 5ml methanol. For the above solution, add remaining amount was make up with 6.8pH Phosphate buffer. This solution contains 1000µg/ml of levofloxacin stock solution. Take 10ml from above solution in 100ml volumetric flask and make up with 6.8pH Phosphate buffer. This solution contains 100µg/ml of drug. From above solution take 1 ml in 10ml volumetric flask and make up with 6.8Ph Phosphate buffer. From this solution pipette out 0.2 ml in 10ml volumetric flask add buffer. This gives 0.2µg/ml Solution. Similarly, preparing the 0.4ml, 0.6ml, 0.8ml and 1ml of solutions in 10ml volumetric flasks Resulting gives, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml solutions. The concentrated solution scanned in UV-Visible Spectrophotometer with absorption maximum is 298nm.

Evaluation of Levofloxacin tablets:

The prepared tablets were evaluated for hardness, thickness and diameter, friability, disintegration time, wetting time, drug content, *in-vitro* dissolution studies, and stability studies.

Hardness:

Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded.

Thickness:

The thickness and diameter of 4 tablets (2 tablets from each batch) were recorded during the process of compression using vernier's calipers.

Friability:

The friability of tablets was determined using Roche friabilator. Four tablets were accurately weighed and placed in the friabilator and operated for 100 Revolutions (25 rpm for 4 min). The tablets were de-dusted and reweighed. Percentage friability was calculated using the following formula:

$$F = (1- W0 / W) \times 100$$

Where, W0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

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Six tablets were tested from each formulation. However, it becomes a great challenge for a formulator to achieve friability within this limit for MDT product keeping hardness at its lowest possible level in order to achieve a minimum possible disintegration time. This test is again not applicable for lyophilized and flash dose tablets, but is always recommended for tablets prepared by direct compression and moulding techniques to ensure that they have enough mechanical strength to withstand the abrasion during shipping and shelf life.

Disintegration time study:

Tablet was put into 100 ml distilled water at 37 ±2°c. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus.

Wetting time study:

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. All the post compression parameters results are shown in table 5.

In Vitro Dissolution Studies:

In-Vitro Release Profile of Formulated Tablets: The dissolution of Levofloxacin tablets was performed in USP type 2 dissolution apparatus. The dissolution medium was 900 ml of gastric simulated fluid pH 1.2 maintained at temperature 37C+ 10 C. The basket was rotated at 50 rpm for 15 min. The sample of 5 ml was withdrawn after every 5 min with maintaining sink condition and its absorbance was measured at 298 nm.

Table 4: Pre compression parameters of formulations F1-F16.

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index
F1	26.5	2.2	2.0	9.09
F2	28.2	2.5	2.2	12.0
F3	29.3	2.7	2.3	14.8
F4	26.7	2.5	2.4	4.0
F5	24.1	2.0	1.8	10.0
F6	25.2	2.4	1.9	20.8
F7	24.3	2.5	2.2	12.0
F8	22.5	2.8	2.4	14.2
F9	20.1	2.1	2.0	4.7
F10	22.0	3.0	2.2	26.6
F11	21.2	2.5	1.9	22.4
F12	23.1	3.0	2.1	29.3
F13	22.2	2.3	2.1	5.1
F14	24.5	2.6	2.2	22.5
F15	25.5	2.8	1.9	28.3
F16	21.2	3.0	2.4	4.8

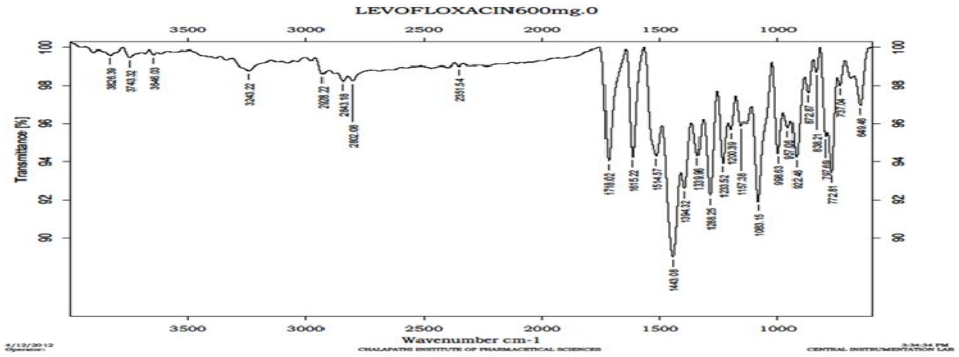

Fig 1: FT-IR Graph for pure drug Levofloxacin hemihydrate.

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Table 5: Post compression parameters of formulations F1-F16:

Formulation code	Hardness (kg/cm^2)	Friability (%)	Disintegration time(sec)	Wetting time(sec)
F1	2.9	0.91	23	42
F2	2.5	0.89	18	40
F3	3.6	0.85	12	39
F4	4.7	0.79	18	37
F5	4.5	0.84	20	32
F6	3.1	0.86	15	31
F7	3.4	0.84	18	35
F8	4.0	0.85	16	36
F9	4.2	0.73	19	32
F10	4.4	0.75	14	36
F11	4.5	0.77	12	35
F12	3.4	0.72	10	30
F13	3.6	0.81	22	38
F14	3.9	0.82	18	36
F15	4.0	0.80	17	34
F16	4.5	0.76	15	33

Table 6: Dissolution profile

Formulation	% release after 2.5 min	% release after 5 min	% release after 7.5 min	% release after 10 min
F1	60.61	71.22	84.14	94.56
F2	64.28	75.51	86.14	95.35
F3	74.12	77.24	88.15	97.45
F4	69.39	78.50	86.51	96.30
F5	70.12	79.21	80.25	95.51
F6	72.11	79.51	81.45	95.66
F7	74.51	80.32	82.25	96.27
F8	70.51	82.14	85.81	96.54
F9	76.24	88.56	90.01	96.71
F10	77.23	78.12	89.12	97.54
F11	78.00	83.60	89.45	98.81
F12	78.72	89.51	94.76	100.01
F13	73.26	83.6	88.61	97.21
F14	75.25	89.71	94.51	98.54
F15	75.12	88.51	92.21	99.0
F16	79.52	90.10	95.6	100.25

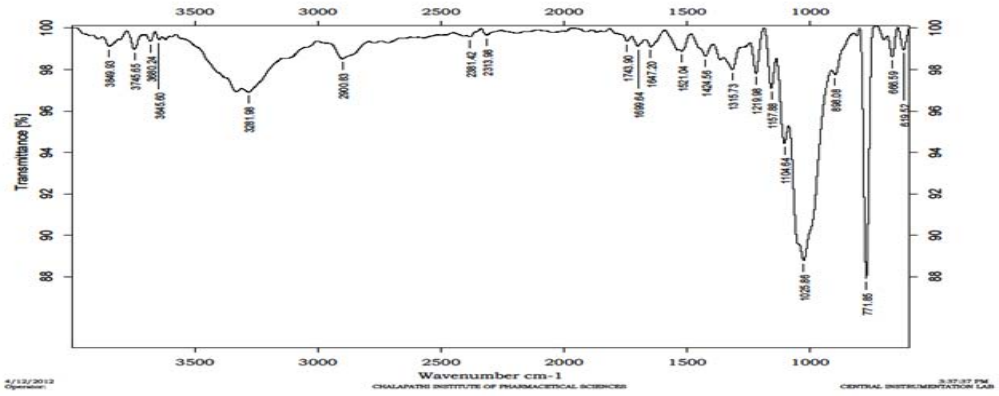

Fig 2: FT-IR graph of Levofloxacin with Microcrystalline cellulose

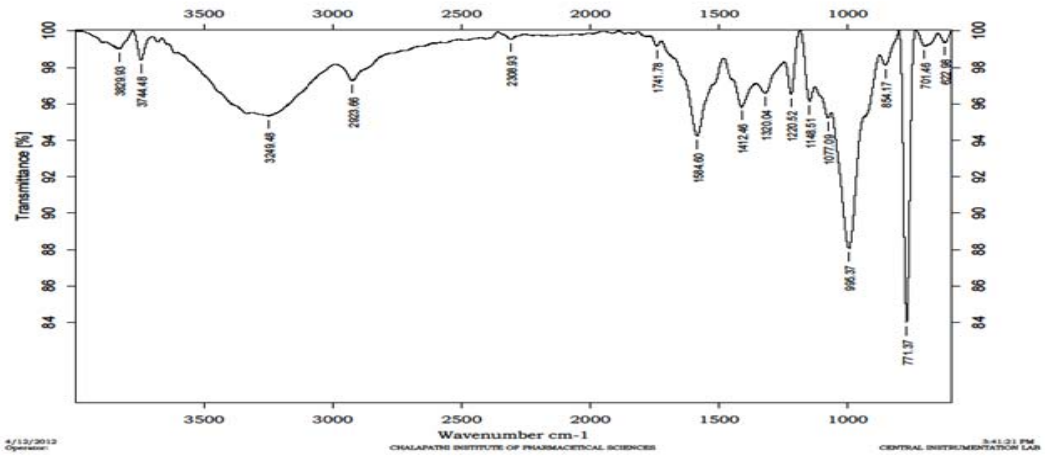

Fig 3: FT-IR graph of Levofloxacin with sodium starch glycolate

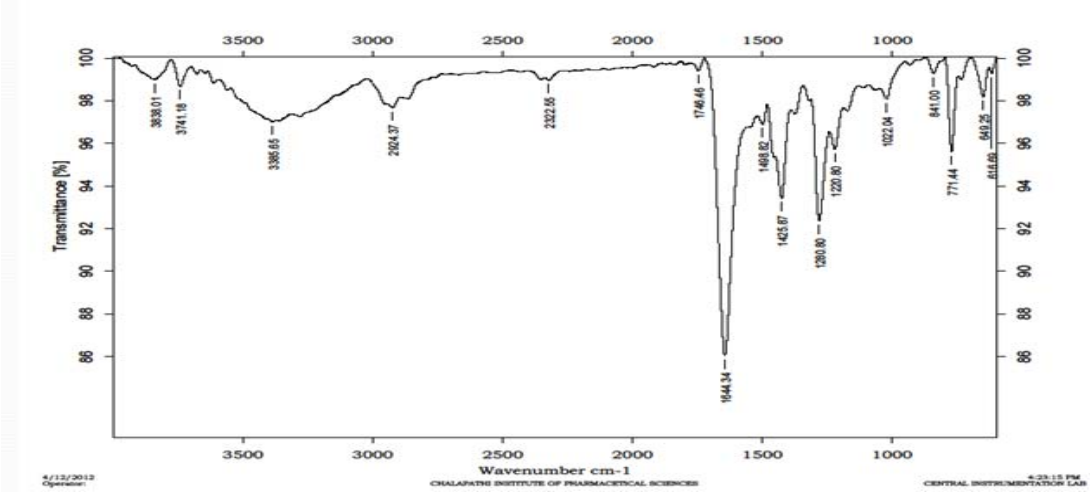

Fig 4: FT-IR graph of Levofloxacin with crosspovidone

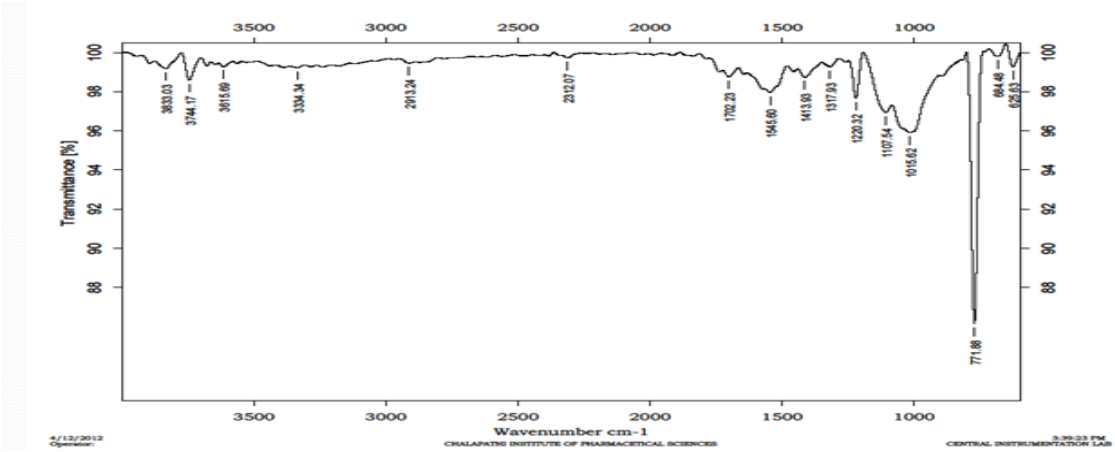

Fig 5: FT-IR graph of Levofloxacin with crosscarmellose sodium

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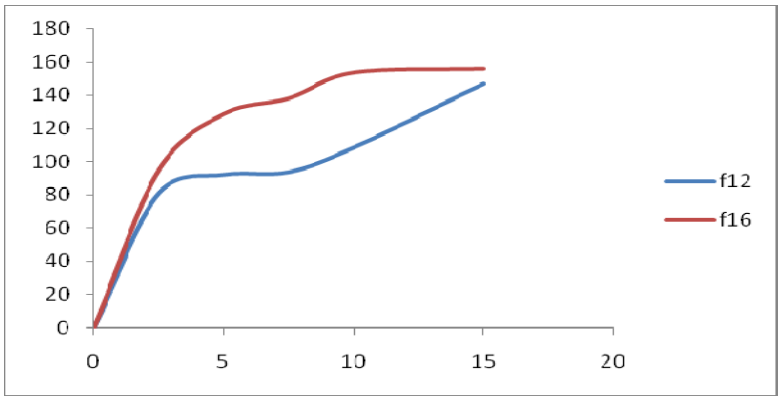
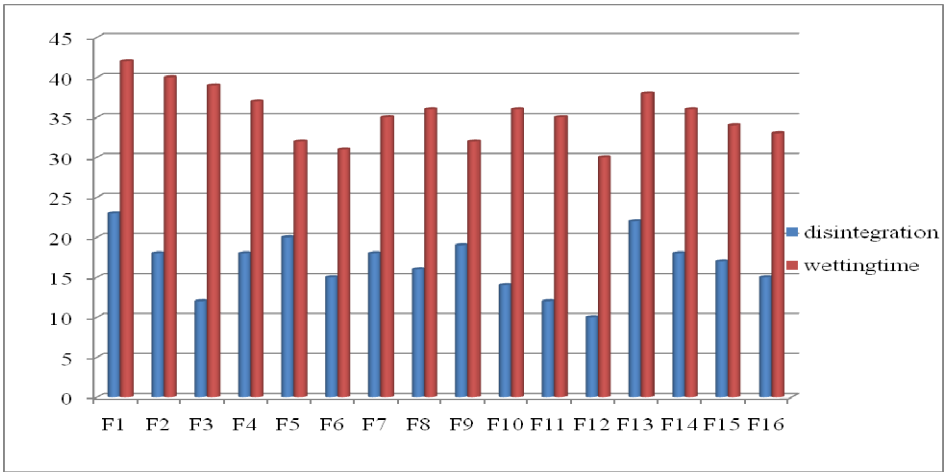
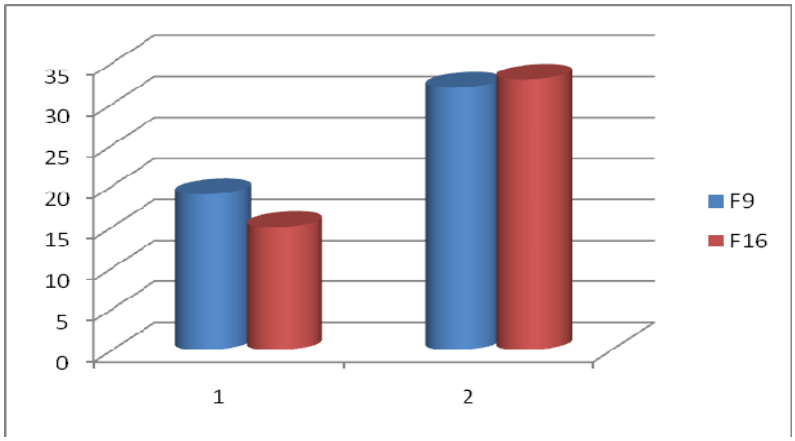


Graph 2: Dissolution profile: comparison of best formulations crospovidone and fenugreek powder.



Graph 3: comparison of disintegration time (DT) and wetting time (WT).



Graph 4: Comparison of disintegration time (DT) and wetting time (WT) of Crospovidone and Fenugreek powder.

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RESULTS AND DISCUSSION

The present study was carried out to prepare the levofloxacin fast dissolving tablets with the intention to release drug rapidly from the tablet and to know which superdisintegrant is best for formulation. Among the synthetic superdisintegrants, Crosspovidone shows best results. Among all four superdisintegrants, Fenugreek powder shows the best results. It is natural superdisintegrant and its preparation was easy and economical. The prepared tablets in all formulations have good mechanical with sufficient hardness and the values lies between 3-5.0 kg/cm^2

The percent friability was less than 1% in all the formulations and the values between 0.25-0.85%. All the tablets from each formulation passed weight variation test, as the percentage weight variation was within the standard limits. The thickness of the tablets in all formulations was uniform. The disintegration time (D.T) and wetting time (W.T) of all formulations are shown in the table. Comparison of disintegration time and wetting time also shown in the graph3. The dissolution data was shown in the table 6. Stability studies were carried out at 25^0C/60% RH and 40^0 C/75% RH for 2 months. All the pre compression and post compression parameters are evaluated for all formulations.

CONCLUSION

Fast disintegrating tablets of Levofloxacin hemihydrate prepared by synthetic and natural superdisintegrants.

The concentrations used for the preparation of tablets were 2%, 3%,4% and 5%.
Among the synthetic superdisintegrants crosspovidone with 5% was best.

After all the formulations, F13-F16 were prepared by natural superdisintegrant Fenugreek powder.

The formulation F16 (concentration 5%) was best in all evaluation parameters.
Stability studies also shows that all the formulations are stable.

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