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RESEARCH ARTICLE

Design and Characterization of Levofloxacin Orodispersible Tablets

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ABSTRACT:
In order to overcome the challenges of the solid unit dosage forms, Fast Dissolving Tablets (FDT) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These novel types of tablets have the ability to dissolve more rapidly when compared to standard solid dosage forms. The main objective of the present study was to develop Oral dispersible tablet formulation containing 150mg of Levofloxacin for the treatment of a number of infections including infection of Joints and bones, respiratory tract infections, urinary tract infections, skin structural infections and typhoid fever etc. In our study, it was observed that all the values of pre-compression and post-compression studies were within the limits.

KEYWORDS: Oral Disintegrating Tablets, Levofloxacin, Superdisintegrants, Stability Studies.

INTRODUCTION:
Oral dispersing tablets are the solid dosage forms that essentially promote faster dissolution of the tablets and thus they promote faster onset of action[1]. The main important characteristic feature of the ODT was to promote rapid dissolution without the use of saliva. Hence due to this reason they were found to acceptable in all population irrespective of their age and gender having difficulty in swallowing of conventional dosage forms[2]. Most of the drugs which are mainly available as the solid unit dosage forms were mainly disintegrated in saliva and then pass down to stomach. Thus the bioavailability of such drug molecule was increased even after hepatic metabolism.

Consumer satisfaction had become the most important parameter of the current millennium, and moment to achieve it has already begun in the pharmaceutical industry.

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An inability or unwillingness to swallow solid oral dosage forms such as tablets and poor taste of medicine are some of the important reasons for consumer dissatisfaction.

Recent developments in technology have presented various alternatives for the patients who may have difficulty in swallowing tablets or liquids. Basically, most of the tablets and capsules were administered with water and this has become inconvenient for the elderly and pediatric patients because of their inability to swallow solid dosage forms. An eight-year-old child with allergies could use a more convenient dosage form of antihistamine syrup. In case of a schizophrenic patient rather than giving atypical antipsychotics, it was wise to promote the conventional dosage form with faster dissolution and onset of action. This conventional dosage form also plays an important role in masking the taste and odor of the H_2 blocker used in radiation therapy for breast cancer[3].

In order to overcome the challenges of the solid unit dosage forms, Fast Dissolving Tablets (FDT) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These novel types of tablets have the ability to dissolve more rapidly when compared to standard solid dosage forms. As per European Pharmacopoeia, the orally dispersible tablet should

disintegrate within three minutes[4]. For the development of such FDT super disintegrants like Crospovidone, Sodium starch glycolate and Pregelatinized starch (Starch-1500) plays an important role in providing instantaneous disintegration of the tablet after putting on the tongue, thereby releasing the drug in saliva. ODT plays an important role in the pre-gastric absorption of the drug from saliva and later the dispersed drug from saliva reaches the stomach and thus due to this reason bioavailability of this drug was improved when compared to solid unit dosage forms. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets[5].

Scope of present work:

Since from the past few years, there has been the increase in demand for more patient compliance dosage forms[6]. Hence due to this reason, the demand for their technologies has been increased rapidly. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with dosing frequency to minimize side effects.

This results in slower dissolution and absorption rates on oral administration and is one of the causes of gastrointestinal side effects. Improvement in drug solubility expected to enhance its bioavailability and reduce local side effects[7].

Difficulty in swallowing (dysphasia) is a common problem of all age groups, especially in case of the elderly and pediatrics, because of physiological changes associated with these groups. Other categories also experience problems in using conventional oral dosage forms include the mentally ill, uncooperative patients, suffering from nausea, sudden episodes of allergic attack or coughing[8]. Sometimes it may be difficult to swallow conventional products due to unavailability of water. These problems led to the development of levofloxacin as mouth dissolving tablets. Which disintegrate and dissolve in saliva without the need for drinking water. The saliva serves to rapidly disperse the dosage form and the dissolved medicament is swallowed along with saliva in a normal way. As the dissolved medicaments along with saliva pass down into the stomach, they are absorbed from the mouth, pharynx, and esophagus. Therefore the bioavailability of levofloxacin is significantly greater than those observed from conventional levofloxacin dosage forms[9].

Levofloxacin is used for the treatment of a number of infections including infection of joints and bones, gastroenteritis, malignant otitis externa, respiratory tract infections, cellulitis, urinary tract infections, anthrax, skin structural infections, typhoid fever and it also used in the treatment of community-acquired pneumonia, chronic bacterial prostatitis, nosocomial pneumonia[10-13].

It has prolonged half-life about 8 hrs. It is a poorly water-soluble drug. When a poorly water-soluble drug administered orally it may cause problems in bioavailability and dissolution rates due to its poor solubility in biological fluids[14-15]. Hence the present work was aimed at increasing the rate of dissolution of Levofloxacin thus providing the faster rate of absorption by adding potential superdisintegrants like Croscarmellosesodium [CCS], crospovidone [CP], and sodium starch glycolate [SSG] in different concentrations[16-18]. To mask the bitter taste of Levofloxacin, Saccharin sodium was used as the sweetening agent. Seven formulations of orodispersible tablets of Levofloxacin were prepared using three different super disintegrants namely Croscarmellose sodium, crospovidone and sodium starch glycolate with three concentrations prepared by direct compression method[19-23]. The prepared Levofloxacin orodispersible tablets using different concentrations were evaluated by *in vitro* drug release studies.

MATERIALS AND METHODS:

Materials:

Levofloxacin was a kind gift from Ethypharma Pvt. Ltd. (Mumbai, India). Sodium starch glycolate, Croscarmellose Sodium, Crospovidone, Avicel and Sodium Saccharin were Obtained from Rajesh Chemicals, Mumbai, India.Mannitol and Magnesium Stearate have obtained from S.D Fine chemicals Mumbai, All Other Chemicals used were of the standard Analytical grade.

Standard curve of Levofloxacin:

Preparation of levofloxacin stock solution:

100 mg of the pure drug of Levofloxacin was dissolved in the 100ml volumetric flask. The drug was shaken with 5ml methanol. For the above solution, add remaining amount was makeup with 6.8 pH Phosphate buffer. This solution contains 1000µg/ml of levofloxacin stock solution. Take 10ml of above solution in a 100ml volumetric flask and makeup with 6.8 pH Phosphate buffer. This solution contains 100µg/ml of drug. From above solution take 1 ml in a 10ml volumetric flask and makeup with 6.8 pH Phosphate buffer. From this solution pipette out 0.2 ml in 10ml volumetric flask add the 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, 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml solutions. The concentrated solution scanned in UV-Visible Spectrophotometer with absorption maximum is 298nm. The results were shown in Table 1. And fig 1.

Standard curve of Levofloxacin:

Table 1: Standard curve of Levofloxacin in Phosphate buffer (pH 6.8)

S.No	Concentration (µg/ml)	Absorbance (298nm)
1	0	0.00
2	2	0.232
3	4	0.465
4	6	0.684
5	8	0.926
6	10	1.126

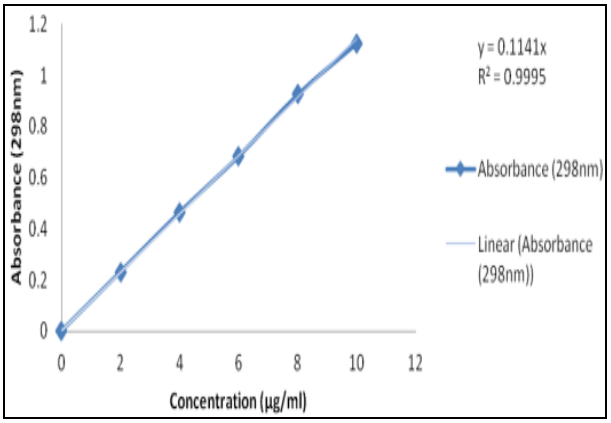

Figure 1: Standard curve of Levofloxacin in Phosphate buffer (pH 6.8)

Preparation of Levofloxacin tablets:

Table 2: Different Formulation of Levofloxacin Oral Dispersible Tablets

Formulation Code	Drug	SSG	CCS	CP	Avicel PH102	Mannitol	sodium saccharin	Magnesium Stearate	Mint flavor
FLOT-1	150	90	-	-	100	45	10	5	q.s
FLOT-2	150	-	90	-	100	45	10	5	q.s
FLOT-3	150	-	-	90	100	45	10	5	q.s
FLOT-4	150	45	45	-	100	45	10	5	q.s
FLOT-5	150	-	45	45	100	45	10	5	q.s
FLOT-6	150	45	-	45	100	45	10	5	q.s
FLOT-7	150	30	30	30	100	45	10	5	q.s

Tapped density:

The tapped density of the levofloxacin powder or granules was calculated by using the following formula[25]

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose:

The angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose of the powder or granules was determined by fixed funnel method to assess the flow property of the powder or granules[26]. The angle of repose (**θ**) was calculated by using the following formula and Limits were represented in Table 3.

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

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[24].

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 400mg and the dose of the drug is 150mg. The different formulations of oral dispersible tablets were shown in Table 2.

Precompression studies of powder blends:

Bulk density:

Bulk density is the ratio between a given mass of powder or granules and its bulk volume. Accurately weighed quantity of granules was carefully transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Bulk density = Mass / Volume

Where,
θ = Angle of repose,
h = Height of the powder cone,
r = Radius of the powder cone.

Table 3: Angle of Repose I.P limits

Sl.No	Angle of Repose	Powder flow
1	< 25	Excellent
2	25 – 3	Good
3	30 – 40	Passable
4	> 40	Very poor

Compressibility Index or Carr's Index:

Carr's Index is measured using the values of bulk density and tapped density.
The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where,
TD = Tapped density
BD = Bulk density

Hausner's Ratio:
It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules. The Hausner's ratio was calculated by using the following formula

Hausner's Ratio = Tapped density/Bulk density

Post compression studies of Levofloxacin tablets:
Hardness is a force required to break a tablet across a diameter. The hardness of the tablet was determined using the Monsanto hardness tester.

Thickness Test:
Ten tablets were randomly selected from each tablet thickness was determined using a Vernier caliper and the reading was recorded in millimeters.

Friability Test:
This test was performed by using the Roche friabilator. The pre-weighed tablets were placed in the friabilator which was then operated for 100rpm, then dusted and reweighed. Here in this study, the samples that lose less than 0.5-1.0% of their body weight were considered to be acceptable. The percent friability was determined using the following formula[27]

$$\text{Friability} = (W_1 - W_2) / W_1 \times 100$$

Where,
W_1 = Weight of ten tablets before test
W_2 = Weight of ten tablets after test

Weight variation:
After the random selection of tablets the average weight of these tablets, was determined. Then later, percentage deviation was determined by calculating the difference between individual weight and the average weight[28]. The percentage deviation was calculated by using the following formula and the Limit values were shown in Table 4.

$$\text{Percentage Deviation} = \frac{\text{Individual weight - Average weight}}{\text{Average weight}} \times 100$$

Table 4: Weight variation Tolerances for uncoated Tablets

S.No	Average weight of Tablets(mg)	Maximum % difference allowed
1	130 or less	± 10
2	130-324	±7.5
3	More than 324	±5

Estimation of drug content:
The term uniformity of dosage unit is defined as the degree of uniformity for substance among dosage units. Ten tablets from each formulation were powdered. The powder equivalent to 150 mg of levofloxacin was weighed and dissolved in distilled water in 100ml standard flasks. From this dilution was prepared and the solution was analyzed at 298 nm using double beam spectrophotometer.

Disintegration time study:
This test was carried out on six tablets using distilled water at 37°C± 2°C was used as disintegration media and the time in seconds taken for complete disintegration of the tablet remaining in the apparatus was measured

Wetting time study:
A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 5 ml of distilled water. Here in this study, the wetting capability of the tablet was determined by placing the tablet on the paper containing the distilled water for few seconds[29]. All the post compression parameters results are shown in Table 6, 7.

In-vitro drug release study:
In vitro release studies were carried out by using USP paddle dissolution test apparatus. 900ml of Phosphate buffer (pH 6.8) was taken in the dissolution vessel and the temperature of the medium was maintained at 37±0.5ºC. 100rpm was maintained, 1 ml of sample was withdrawn at predetermined time intervals for 0, 1, 3, 6, 9, 12 and 15 mints. The same volume of the fresh medium was replaced. The samples were analyzed at 298nm by using a UV spectrophotometer[30-31]. The dissolution data obtained were plotted as percentage drug release versus time.

FT-IR studies:
It was used to study the It was used to study the interactions between the drug and superdisintegrants. The drug and superdisintegrants must be compatible with one another to produce a product stable, efficacious and easy to administer and safe. IR spectral analysis for drug, superdisintegrants was carried out. If there is no change in peaks of mixture when compared to pure drug, it indicates the absence of interactions[32].

Stability study:
This study mainly meant to determine the shelf life of the formulation and it was performed according to ICH guidelines. The optimized formulation was wrapped in the laminated aluminum foils and was placed in the accelerated stability chamber (6CHM-GMP, Remi Instrument Ltd., Mumbai) at elevated temperature and humidity conditions of 40°C/ 75% RH and a control sample was placed at an ambient condition for a period of three months. Sampling was done at a predetermined time of initial 0, 1, 2 and 3 months interval respectively. Finally, the samples were tested for the drug content, *in vitro* drug release.[22-23]

RESULT AND DISCUSSION:

Levofloxacin oral disintegrating tablets were prepared by direct compression method using Sodium starch glycolate, Croscarmellose sodium and Crospovidone as super disintegrants. The physical characteristics of the powder blends such as bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose were determined. The results are given in Table 5. Bulk density (0.312 to 0.352 gm. /cm^3) and Tapped density (0.333 to 0.384 gm. /cm^3) values are within the limits, indicating that the powder blends have the required flow property for direct compression. The values obtained for angle of repose for all formulations are tabulated in table the values were found to be in the range from 31.38-39.48°. This indicates good flow property of the powder blend. Compressibility index (6.30 to 10.93) and Hausner's ratio (1.067 to 1.122) values are within the limits, indicating that the powder blends have the required flow property for direct compression.

Table 5: Precompression studies of powder blend

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	FLOT-1	0.334	0.375	32.26	10.93	1.122
2	FLOT-2	0.346	0.372	34.15	6.98	1.075
3	FLOT-3	0.328	0.362	33.82	9.39	1.103
4	FLOT-4	0.312	0.333	31.38	6.30	1.067
5	FLOT-5	0.333	0.368	35.07	9.51	1.105
6	FLOT-6	0.352	0.384	35.07	8.33	1.090
7	FLOT-7	0.326	0.354	39.48	7.90	1.085

Table 6: Post compression studies of Levofloxacin oral dispersible Tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content
1	FLOT-1	2.45	0.37	0.164	99.7	98.12
2	FLOT-2	2.34	0.37	0.228	99.2	96.29
3	FLOT-3	3.42	0.37	0.236	99.8	97.54
4	FLOT-4	2.92	0.37	0.267	99.8	97.27
5	FLOT-5	2.65	0.37	0.224	99.6	96.48
6	FLOT-6	3.23	0.37	0.254	99.5	98.34
7	FLOT-7	2.86	0.37	0.253	99.9	98.84

Evaluation of Levofloxacin oral disintegrating tablets:

The compressed tablets were evaluated for physical properties and the results are tabulated in Table 6.

Table 7: Post compression studies of Levofloxacin oral dispersible Tablets

S.No	Formulations	Disintegration time (sec)	Wetting time (sec)
1	FLOT-1	25	17
2	FLOT-2	23	16
3	FLOT-3	32	17
4	FLOT-4	22	15
5	FLOT-5	25	15
6	FLOT-6	23	16
7	FLOT-7	20	14

Hardness, friability and weight uniformity of tablets and Estimation of Drug Content:

The various batches of the Oral dispersible tablets of hardness values are found within limits and it indicates good strength of the Oral dispersible tablets. Tablet mean thicknesses were almost uniform in the all formulations and were found to be in the range of 0.37mm. Friability values are found to be less than 1% in all cases and considered to be satisfactory. All this tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients. The values were mentioned in Table 6 and 7.

Disintegration time study:

The disintegration time (D.T) of all formulations is shown in the Table 7. And Fig 2.

Wetting time study:

The wetting time (W.T) of all formulations is shown in the Table 7.And Fig 3.

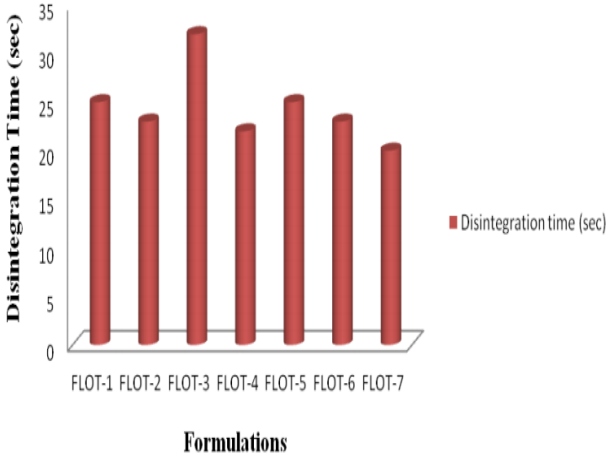

Figure 2: Disintegration time of Different formulations

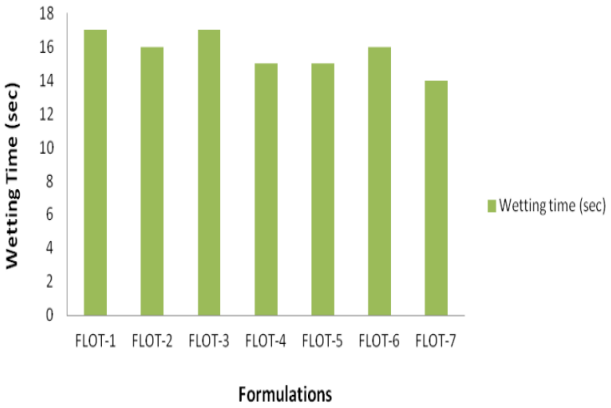

Figure 3: Wetting time of different formulations

IR Spectral analysis:

The IR Spectral studies of pure levofloxacin, Crospovidone, Sodium starch glycolate and CCS were carried out to study the interaction between the drug and super disintegrants used. It showed that IR spectrum of pure Levofloxacin and superdisintegrants were similar fundamental peaks and patterns. The results proved that there were no significant interactions between the drug and super disintegrants. The results are shown in Fig 4 - 8.

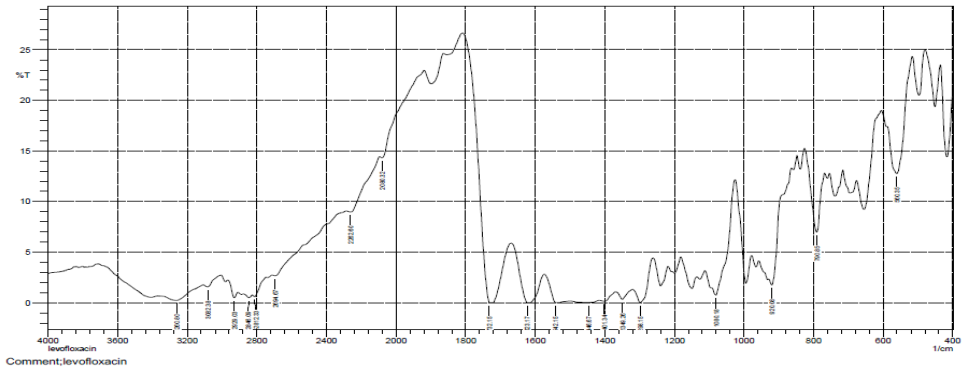

Figure 4: FTIR spectrum of Levofloxacin

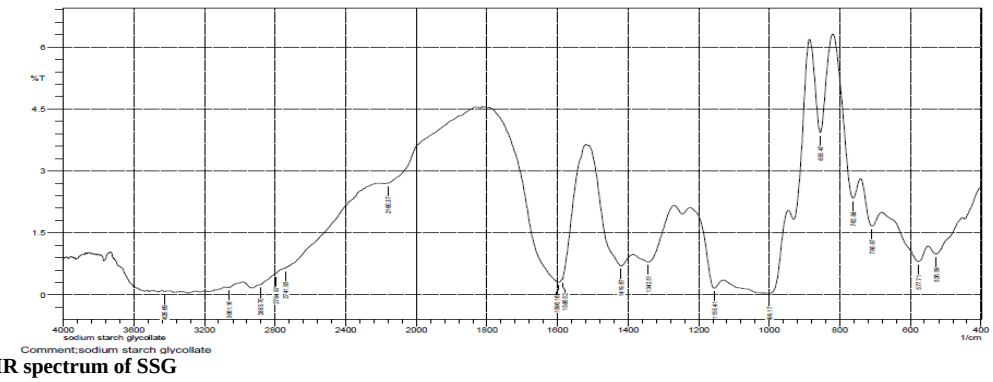

Figure 5: FTIR spectrum of SSG

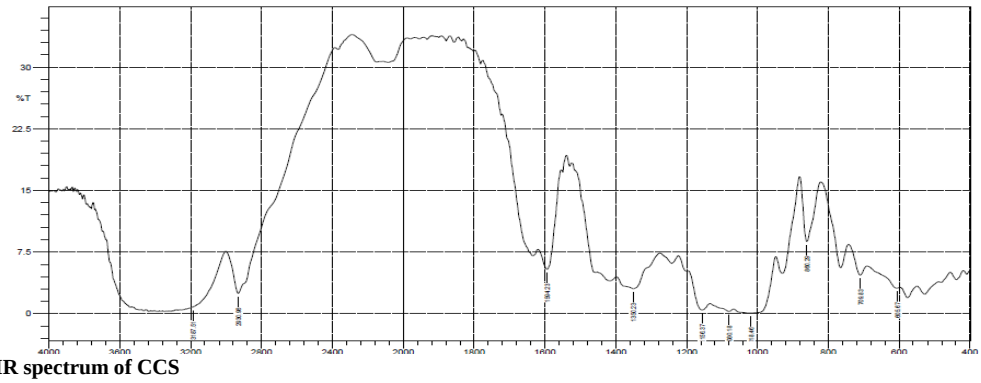

Figure 6: FTIR spectrum of CCS

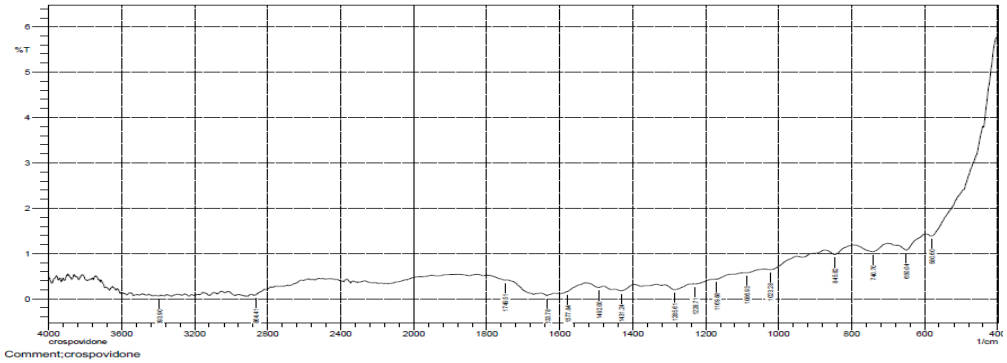

Figure 7: FTIR spectrum of CP

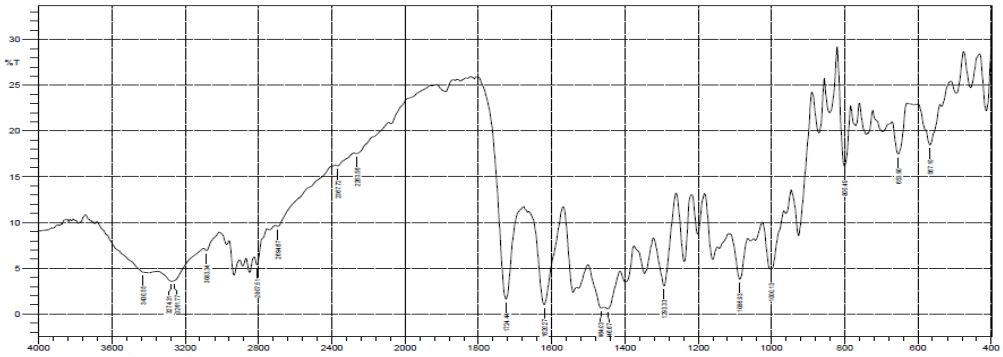

Figure 8: FTIR spectrum of Levofloxacin +SSG+CCS+CP

Invitro drug release study:

Tablets of all the formulations were subjected to in-vitro release studies .The *in vitro* drug release profile of tablets from each batch (FLOT-1 to FLOT-7) was carried in phosphate buffer (pH 6.8) for 15 mints by using paddle type of device. From the *in vitro* dissolution data, the FLOT-7 formulation was found that the drug release is best and the cumulative % of drug release was 96.10 % respectively when compared to other formulation. The % drug release of different formulation was represented in Table 8 and fig 9, 10.

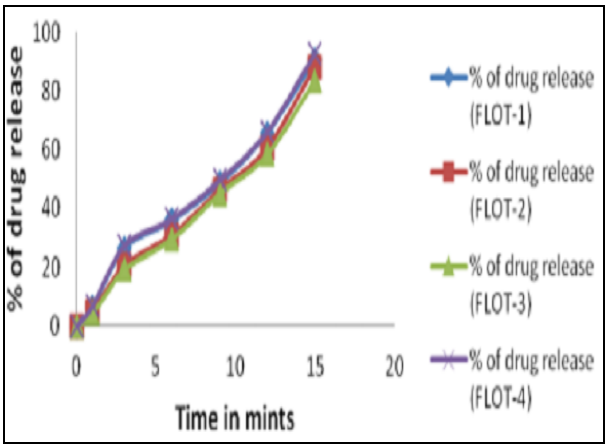

Figure 9: Comparative dissolution study of different formulations (FLOT-1, 2, 3, 4)

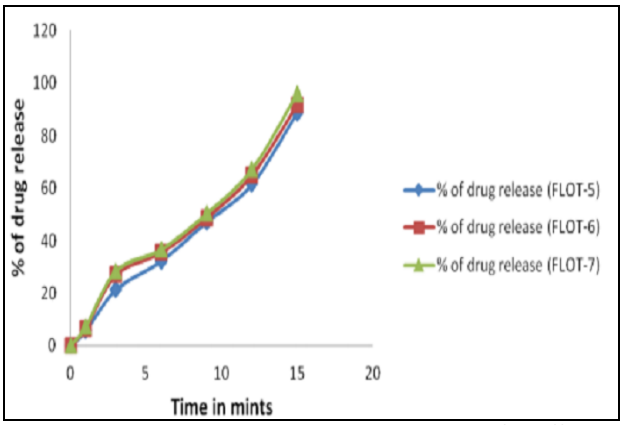

Figure 10: Comparative dissolution study of different formulations (FLOT-5, 6, 7)

Accelerated stability study:

Levofloxacin optimized formulation F07 was found to be stable during accelerated stability studies for drug content 98.84, 98.75, 98.68 and 98.46 % at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. *In vitro* drug release studied and found to be 96.51, 95.94, 94.16, and 92.35% at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. Results obtained were shown in Table 9. Finally, it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 % for three months. It may be inferred that there was no degradation of physical properties and change in the matrix system of the formulation.

Table 8:Comparative dissolution study of different formulations with various ratios of Super disintegrants

S.No	Time (mints)	% of drug release (FLOT-1)	% of drug release (FLOT-2)	% of drug release (FLOT-3)	% of drug release (FLOT-4)	% of drug release (FLOT-5)	% of drug release (FLOT-6)	% of drug release (FLOT-7)
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	6.47	5.05	4.315	6.947	5.684	6.736	7.263
3	3	26.61	20.63	19.15	27.42	21.31	27.05	28.52
4	6	36.00	31.15	29.57	36.52	32.21	35.47	36.63
5	9	48.57	46.26	44.89	49.57	47.05	48.73	50.36
6	12	65.73	60.63	58.21	66.10	61.47	65.00	67.26
7	15	90.68	88.10	83.31	92.78	88.73	91.84	96.10

Table 9:Results of Accelerated stability study of optimized formulations

	Optimized formulation	
	Drug content (%)	**% drug release**
Initial	98.84	96.51
One month		
Ambient	98.36	96.04
40^0c / 75%RH	98.75	95.94
Two month		
Ambient	98.21	95.46
40^0c / 75%RH	98.68	94.16
Three month		
Ambient	98.05	93.75
40^0c / 75%RH	98.46	92.35

CONCLUSION:

The main objective of the present study was to develop Oral dispersible tablet formulation containing 150mg of Levofloxacin for the treatment of a number of infections including infection of Joints and bones, respiratory tract infections, urinary tract infections, skin structural infections and typhoid fever . In our study, it was observed that all the values of Precompression and post-compression studies were within the limits. The *in vitro* dissolution data, FLOT-7 (combination of different superdisintegrants) formulation was found that the drug release is best and the cumulative % of drug release was 96.10 % respectively when compared to other formulation.

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