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Formulation and Evaluation of Oral Fast Disintegrating Tablets of Delafloxacin

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Abstract

The present study is to formulate and evaluate oral fast disintegrating tablets of Delafloxacin by direct compression method. In the present study an attempt has been made to prepare oral fast Disintegrating tablets of Delafloxacin using Crospovidone and cross linked PVP to increase the rate of drug release from dosage form to increase the dissolution rate. Direct Compression method was used to formulate the tablets. All the formulations were showed the acceptable flow properties and the pre compression parameters like Bulk density, Tapped density and Carr's compressibility index and Hausner ratio. The post compression parameters like Weight variation, friability, hardness, disintegration, wetting time, water absorption ration and In vitro dissolution profile values were found to be within specified limits. From the data obtained, it is observed from the formulation F3, shows Disintegration time in 30 seconds and the Percentage drug release is of 99% at the end of 14 min which satisfied all the tablet evaluation parameters for oral fast disintegrating tablet.

Keywords

Delafloxacin, Oral fast disintegrating tablets, cros povidone, cross linked PVP.

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INTRODUCTION:

The oral route is the most preferred route for administration of therapeutic agents because of ease of administration, accurate dose, self-medication and patient compliance. In this regard, tablets and capsules are most preferred dosage forms for oral route. But these dosage forms are difficult to administer to pediatrics and geriatrics. Hence, oral fast disintegrating tablets are favored for its ease of administration and improvement in therapeutic efficacy of dosage form [1-3].

Oral fast disintegrating tablets disintegrate and/or dissolve in the mouth (in saliva) within a few seconds without any need to administer it with liquid. They are also called mouth dissolving, oro-dispersible, orally disintegrating and fast melting tablets. [4,5].

Delafloxacin is a fluoroquinolone antibiotic which has been used in trials studying the treatment and basic science of Gonorrhea, Hepatic Impairment, Bacterial Skin Diseases, Skin Structure Infections, and Community Acquired Pneumonia, among others. It was approved in June 2017 under the trade name

Baxdela for use in the treatment of acute bacterial skin and skin structure infections. [6].

MATERIAL AND METHODS

Materials

Delafloxacin and Crospovidone were obtained as a gift sample from Pharma train, Hyderabad, India. Cross linked PVP, Aerosil, Mannitol, Aspartam, Mg. Stearate was gift sample from Sun life sciences, Hyderabad. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications.

Standard Calibration Curve of Delafloxacin 6.8phosphate buffer

27.22g of monobasic potassium phosphate was weighed and diluted up to 1000 ml to get stock solution of monobasic potassium phosphate. 8g Sodium hydroxide was weighed and diluted up to 1000ml to get 0.2M sodium hydroxide solution. 50 ml of the monobasic potassium phosphate solution was taken from the stock solution in a 200-mL volumetric flask and 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then water was used to make up the volume.

Determination of λ_{max} of Delafloxacin in 6.8 phosphate buffer:

Procedure:

Working standard: 100mg of Delafloxacin was weighed and dissolved in 10ml Methanol and then make up to a volume of 100ml with 6.8 phosphate buffer it gives 1000µg/ml concentrated stock solution.

Dilution 1: From the working standard solution 10ml was diluted to 100ml with 6.8 phosphate buffer it will give 100µg/ml concentrated solution.

Dilution 2: From the dilution1, 10ml solution was diluted to 100ml with 6.8 phosphate buffer it will give 10µg/ml concentrated solution.

This solution was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted. the corresponding wavelength having highest absorbance is noted as λ_{max}.

Standard Calibration curve of Delafloxacin in phosphate buffer pH 6.8 solution:

Working standard: 100mg of Delafloxacin was weighed and dissolved in 10ml Methanol and then make up to a volume of 100ml with 6.8 phosphate buffer it gives 1000µg/ml concentrated stock solution.

Dilution 1: From the working standard solution 10ml was diluted to 100ml with 6.8 phosphate buffer it will give 100µg/ml concentrated solution.

From the dilution 1, Aliquots of 0.5, 1, 1.5, 2 and 2.5ml of solution were pipette out in to 10ml volumetric flask. The volume was made up to the mark with phosphate buffer pH6.8. These dilutions give 5, 10, 15, 20 and 25µg/ml concentrations of Delafloxacin respectively. The absorbance was measured in the UV-visible spectrophotometer at 295 nm using distilled water as blank and graph of concentration versus absorbance was plotted. The absorbance data for standard calibration curves are given in the results table.

PREPARATION OF DELAFLOXACIN ORAL FAST DISINTEGRATING TABLETS

Direct compression method:

Oral disintegrating tablets of Delafloxacin were prepared by direct compression method.

All the ingredients were powdered separately and passed through # 40 mesh sieve separately. The drug and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and mixed for further two minutes and the tablets were compressed using 6-8mm flat round punches to get tablets of 450 mg weight.

Table 1: Formulae of Delafloxacin oral fast disintegrating Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Delafloxacin	350	350	350	350	350	350	350	350	350
Crospovidone	30	40	50	-	-	75	-	-	90
Cross linked PVP	-	-	25	50	75	-	60	-	-
Magnesium Stearate	15	15	15	15	15	15	15	-	-
Aerosil	5	5	5	5	5	5	5	5	5
Mannitol	45	35	-	25	-	-	15	90	-
Aspartam	5	5	5	5	5	5	5	5	5
Total wt (mg)	450	450	450	450	450	450	450	450	450

EVALUATION OF ORAL FAST DISINTEGRATING TABLETS OF DELAFLOXACIN

I. Pre compression studies:

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

1. 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 (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

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

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

2. Tapped density (D_t): It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc 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

3. Carr's index (%): The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

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

5. Angle of repose (θ): It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

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

Method: The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose $\geq 40^{o}$ suggests a poorly flowing material.

II. Post compression studies

1. Weight variation: Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

2. Hardness and Friability: Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

3. Content uniformity test

Ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of Delafloxacin was transferred to a 100 ml volumetric flask and 10 ml methanol is added. The drug is extracted in methanol by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with 6.8 phosphate buffer and the liquid is filtered. From prepared solution take 0.1ml soluion in 10ml volumetric flask and make up to mark with 6.8 phosphate buffer. The Delafloxacin content was determined by measuring the absorbance at 295 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

4. Wetting time and Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed.

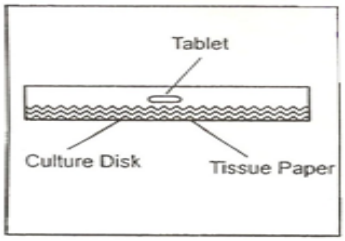

Figure 1: Schematic representation of wetting time / water absorption determination

Water absorption ratio 'R' was determined using following equation

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

Where, W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption

5. In vitro dispersion time

Tablet was added to 10 ml of pH 6.8 phosphate buffer solution at 37 ± 0.5° C. Time required for complete dispersion of a tablet was measured.

6. Dissolution study

In vitro dissolution of Delafloxacin oral fast disintegrating tablets was studied in USP XXIII type-II dissolution apparatus (LABINDIA) employing a paddle stirrer at 50 rpm. 900 ml of 6.8 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5° C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 295 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Delafloxacin released was calculated and plotted against time.

STABILITY STUDIES:

In designing a solid dosage form it is necessary to know the inherent stability of the drug substance, to have an idea of what excipients to use, as well as how best to put them together with the drug and to know that no toxic substance is formed. Limits of acceptability and therefore compromises must be reasonably defined. Because the measurements of these aspects of stability as well as determination of shelf life or expiration date for the final dosage form require long term stability studies for confirmation, they can be expensive and time consuming. Consequently, it is necessary to define those study designs and conditions that show the greatest probability of success. The objective therefore of a stability study is to identify and help avoid or control situations where the stability of the active ingredient may be compromised. For a drug substance to be developed into a tablet dosage form, this objective may be achieved by investigating the stability of the drug under the following three categories, (1) solid state stability of drug alone, (2) compatibility studies in presence of excipients, (3) solution phase stability.

Rationale for stability studies:

- There may be chemical degradation of active drug leading to a substantial lowering of the quantity of therapeutic agent in the dosage form.
- Although chemical degradation of the active drug may not be expensive, a toxic product may be formed in the decomposition process.
- Instability of drug product can lead to substantial lowering in the therapeutic efficiency of the dosage form.

Table 2: Stability Storage Conditions

Stability Storage Category	Testing schedule for Physical and Chemical attributes
LONG TERM 25°C ± 2°C / 60% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.
ACCELERATED 40°C ± 2°C / 75% ± 5% RH	1, 2, 3 & 6 Months
INTERMEDIATE 30°C ± 2°C / 60% ± 5% RH	3, 6, 9 & 12 Months
ZONE IV 30°C ± 2°C / 70% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.

RESULTS AND DISCUSSION

Construction of Standard calibration curve of Delafloxacinin 6.8 phosphate buffer:

The absorbance of the solution was measured at 238nm, using UV spectrometer with water as blank. The values are shown in below table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 5 to 25 µg/ml

Table 3: Calibration curve for Delafloxacinin 6.8phosphate buffer:

Concentration (µg/ml)	Absorbance
0	0
5	0.115
10	0.237
15	0.345
20	0.471
25	0.583

Standard plot of Delafloxacin by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown Fig No.3

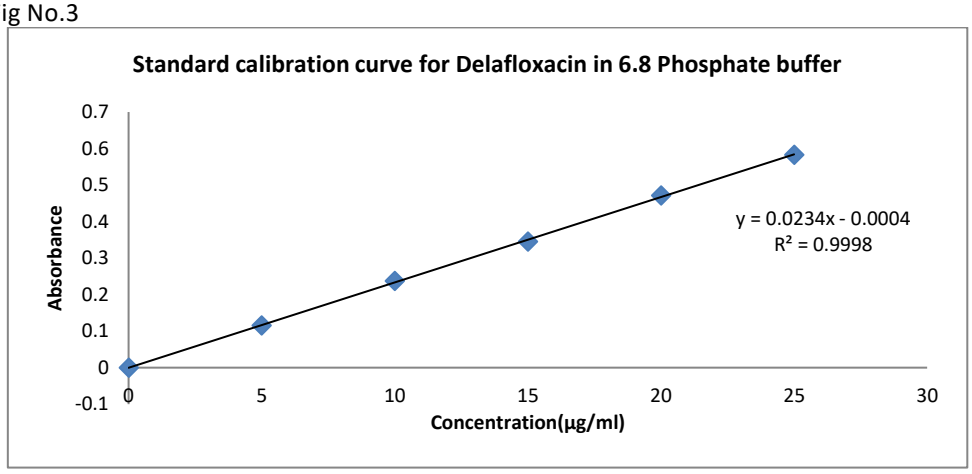

Figure 2: Standard calibration curve of Delafloxacin in 6.8 phosphate buffer

Inference: The standard calibration curve of Delafloxacin in 6.8 phosphate buffer showed good correlation with regression value of 0.999

Table 4: Pre compression studies of Delafloxacin oral disintegrating tablets

Formulation code	Bulk density	Tapped density	Cars index	Hausner's ratio	Angle of repose
F1	0.40	0.48	32.7	1.20	1.20
F2	0.39	0.48	34.95	1.22	1.22
F3	0.50	0.58	28.72	1.15	1.15
F4	0.44	0.50	28.01	1.13	1.13
F5	0.37	0.41	25.45	1.11	1.11
F6	0.37	0.41	33.1	1.11	1.11
F7	0.36	0.39	26.56	1.08	1.08
F8	0.41	0.45	31.84	1.11	1.11
F9	0.39	0.47	28.89	1.22	1.22

Inference:

- The blends prepared for direct compression of tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table 4.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 25.45-34.95˚ which

indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Table 5: Post compression studies of Delafloxacin oral fast disintegrating tablets

Formulation Code	% weight variation	Thickness (mm)	% friability	% Drug Content	Hardness (Kg/cm^2)	Disintegration time (Sec)	Dispersion time(Sec)	Water absorption ratio
F1	pass	4.03	0.143	98.9	3.6	46	32	78.6
F2	pass	3.93	0.110	100.2	3.7	39	27	81.3
F3	pass	4.06	0.142	101.3	3.5	30	23	84.4
F4	pass	4.06	0.151	102.3	3.3	60	42	87.1
F5	pass	4.03	0.62	100.1	3.0	53	36	89.5
F6	pass	4.1	0.154	100.7	3.6	23	17	91.5
F7	pass	3.99	0.23	99.3	3.4	40	28	92.7
F8	pass	4.15	0.19	100.2	3.3	30	23	93.9
F9	pass	4.04	0.17	99.7	3.5	24	16	98.0

Table 6: dissolution profile

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1 N HCL
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	2, 4, 6, 8, 10, 12, 14, 16, 18 and 20minutes
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	295nm

Note: 5 ml of sample was with draw at each time point & replace the same volume of 6.8 phosphate buffer preheated to 37± 0.5 ºC

Table 7: Dissolution data of various oral fast disintegrating tablets of Delafloxacin

TIME (min)	% DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	17	24	24	14	16	22	17	9	24
4	24	33	35	21	22	31	25	15	36
6	35	46	53	26	28	39	33	19	42
8	41	57	68	31	34	47	46	25	51
10	52	65	81	35	42	56	58	30	63
12	59	71	95	40	49	67	64	34	75
14	67	76	99	47	57	75	67	39	87
16	75	89		54	64	81	74	43	98
18	79	93		59	71	85	80	48	
20	85			62	79	91	84	53	

Table 8: Correlation Coefficient (r) Values in the Analysis of dissolution data as per Zero order and First Order Models

Formulation Code	R^2 Values	
	Zero Order	First Order
F1	0.984	0.991
F2	0.963	0.996
F3	0.982	0.875
F4	0.981	0.986
F5	0.992	0.957
F6	0.972	0.966
F7	0.967	0.99
F8	0.992	0.997
F9	0.984	0.775

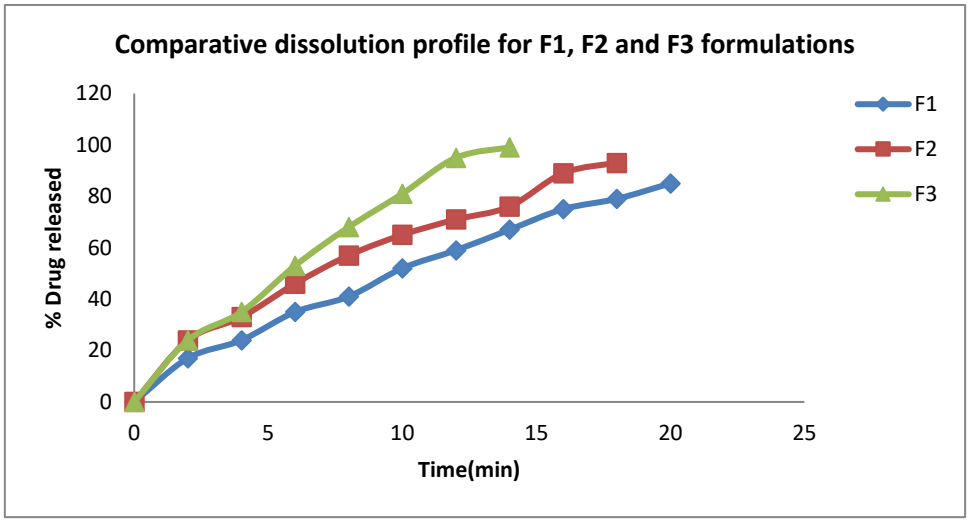

Figure 3: Comparative dissolution profiles for F1, F2 and F3 formulations

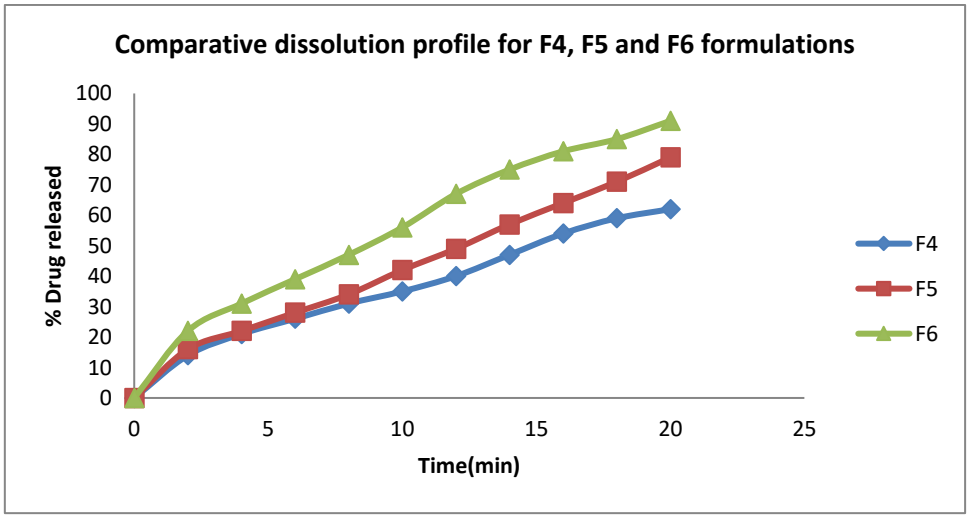

Figure 4: Comparative dissolution profiles for F4, F5 and F6 formulations

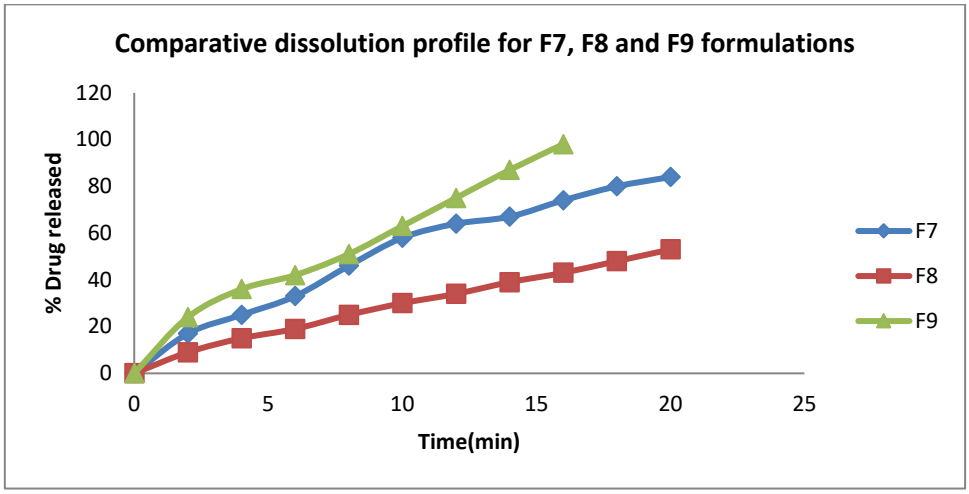

Figure 5: Comparative dissolution profiles for F7, F8 and F9 formulations

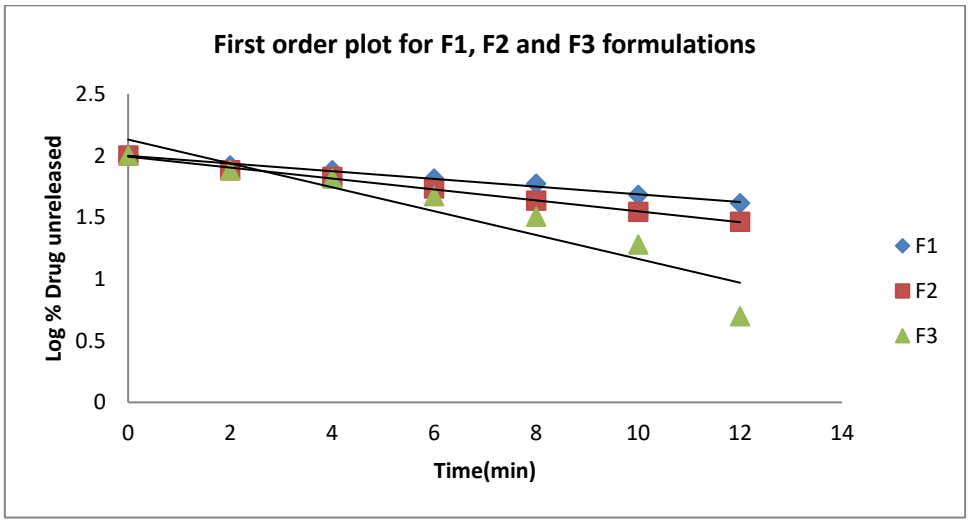

Figure 6: First order plot for F1, F2 and F3 formulations

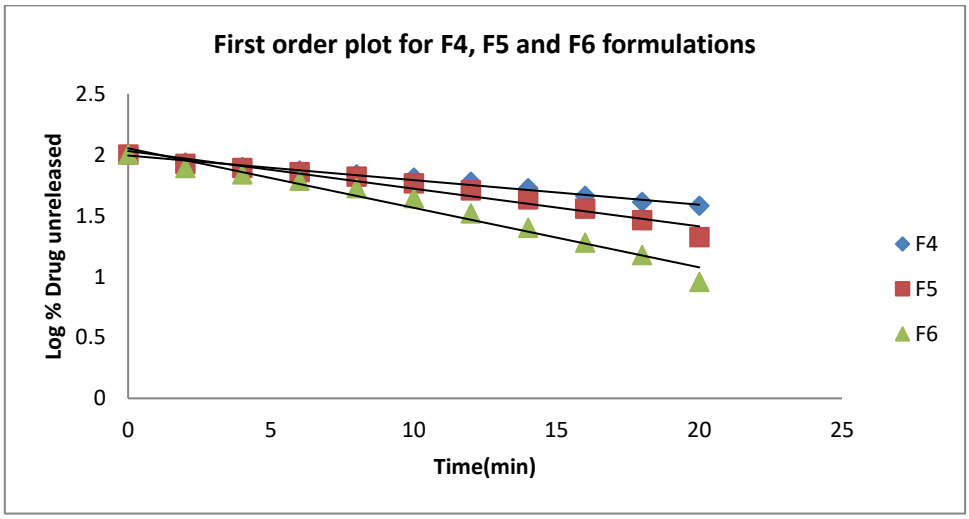

Figure 7: First order plot for F4, F5 and F6 formulations

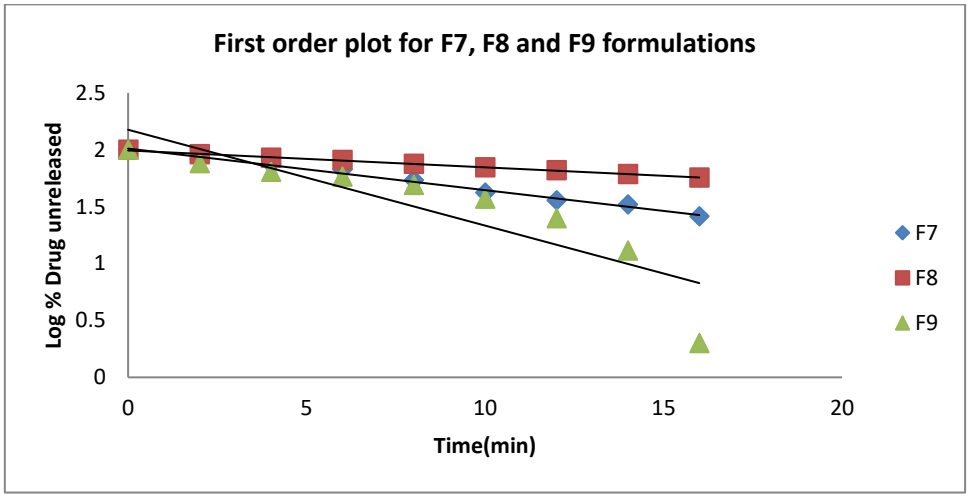

Figure 8: First order plot for F7, F8 and F9 formulations

Inference:
In vitro drug release study was carried out and based on the results; F-3 was identified as the best formulation among all the other formulations.

STABILITY STUDIES OF PHYSICAL AND CHEMICAL PARAMETERS:
Selected formulation F3 was strip packed and stored at 40°C ± 2°C / 75% ± 5% RH or a period of 3 months. Samples were analyzed after storage for 1month and evaluated.

Table 9: *In-vitro* release profile of F3 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

Time(min)	Initial	1 Month	2 Month	3 Month
0	0	0	0	0
2	24	23	23	24
4	31	30	30	30
6	53	53	53	53
8	68	67	67	67
10	81	80	80	81
12	95	94	94	94
14	99	99	99	99

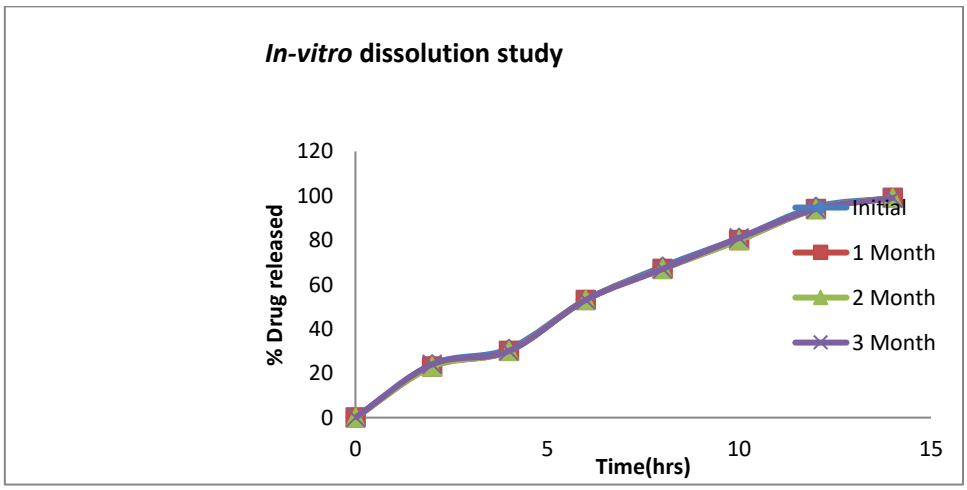

Figure 9: *In-vitro* release profile of F3 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

SUMMARY AND CONCLUSION

1. Suitable analytical method based on UV-Visible spectrophotometer was developed for Delafloxacin. λ_{max} of 295 nm was identified in 6.8phosphate buffer.
2. Direct compression method was established to manufacture oral fast disintegating tablets of Delafloxacin.
3. Oral fast disintegating tablets of Delafloxacin were successfully prepared using crospovidone and cross linked PVP.
4. In the present study, oral disintegating tablets were prepared by direct compression method.
5. Evaluation parameters like hardness, friability, weight variation and drug content indicate that values were within permissible limit for all formulations.
6. *In vitro* drug release study was carried out and based on the results; F-3 was identified as the best formulation among all the other formulations.
7. The crospovidone and cross linked PVP used formulation has shown better release profile than compared with other formulations.

Thus, we are able to achieve our objective of preparing oral disintegrating tablets of Delafloxacin with minimum excipients and simple method of manufacture.

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