DESIGN AND DEVELOPMENT OF PRULIFLOXACIN FORMULATIONS BY CO-CRYSTALLIZATION TECHNIQUE

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ABSTRACT

The present study was undertaken with an aim to formulate Prulifloxacin immediate released tablet by co-crystal technique for the emergency treatment of traveller's disease such as diarrhoea, typhoid as well as UTI infection. Conventional prulifloxacin tablets which are available in market have low solubility as well as bioavailability. To overcome these problems there is a need to develop immediate release tablet, which improves the solubility as well as bioavailability by using co-crystal technique. The purpose of this study was to investigate co-crystal by using different ratios of co-crystal formers as well as different concentration of superdisintegrants sodium starch glycolate, croscarmelose sodium and crospovidone in promoting tablet disintegration and drug dissolution of Prulifloxacin immediate release tablets. The efficiency of superdisintegrants was tested, by considering three concentrations, viz., like 0.6%, 1.2%, and 1.8% in the formulations. The dissolution was carried out in USP apparatus II at 50 rpm with 0.1 N HCL as a dissolution medium. The dissolution rate of the drug Prulifloxacin was found highly dependent on the particle size of superdisintegrants, on the solubility of drug and also on the type of superdisintegrant in the dissolution medium. There was no effect of the diluents (Lactose monohydrate) on the disintegration of different concentration of superdisintegrants. These results suggest that, the dissolution profile of the formulation containing 1.8% croscarmelose sodium (F6*) and lactose monohydrate as a diluents shows good dissolution profile compared to other batches as well as marketed product.

Keywords: Disintegration, Co-Crystallization, Immediate Release, Co-Formers

INTRODUCTION

Co-crystal incorporates pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Co-crystal has regained attention as attractive alternate solid forms for drug development. Physicochemical properties of pharmaceuticals can be improved by obtaining co-crystal using co-crystallisation with pharmaceutically acceptable (GRAS) compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility hygroscopicity , compaction behaviour[1] [2 The components in a co crystal exist in a definite stoichiometric ratio, and assemble via non covalent interactions such as hydrogen bonds, ionic bonds, or van der waals interactions rather than by ion pairing. Generally, co- crystals in their pure states are solids at room temperature and by convention, these normally excludes salts. Co-crystals can have different properties than the crystal of individual components. Further, co-crystals have different crystal structures than the pure components, contain different intermolecular packing patterns, and as such they often exhibit widely different physical properties than the pure components, co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot formed due to the absence of ionisation sites in the API [3][4]. Co-crystals having advantages like stable crystalline form (as compared to amorphous solids), no need to make or break covalent bonds, theoretical capability of all types of API molecules (weakly ionisable/non-ionisable) to form co-crystals, the existence of numerous potential counter-molecules (food additives, preservatives, pharmaceutical excipient, and other APIs), the only solid form that is designable via crystal engineering patentable expanding IP portfolios and can be produced using solid-state synthesis green technologies high yield, no solvent or by-products.

Immediate Release Tablet

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after adminstration. The basic approach used in development tablets is the use of superdisintegrants like Cross linked carboxymelhylcellulose (Croscarmelose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone(Polyplasdone) etc. which provide instantaneous disintegration of tablet after administration[5].

Advantages:

1. Improved compliance
2. Improve stability/ bioavailability
3. Suitable for controlled/ sustained release actives
4. Allows high drug loading
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and ppackeging machinery
7. Cost effective
8. Improved solubility of the pharmaceutical composition
9. Decreased disintegration and dissolution times for immediate release oral dosage forms

Disadvantages:

1. The tablets usually have insufficient mechanical strength. Hence carefull handling is required.
2. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly

MATERIALS AND METHODS

Chemical Reagents

Prulifloxacin was purchased from acetonitrile and other chemicals were used from dr. d. y. patil college of pharmacy laboratory.

CHARACTERIZATION METHODS

1. The Infrared absorption spectrum was obtained using infrared spectrometers (model- Nicolet 380) in the region of 4000-650. All the samples were compressed into disc of 10-15 mm diameter.
2. UV scanning was done for 10 mcg/ml drug solution from 200-400nm in 0.1 N HCL as a blank using double beams UV/VIS spectrophotometer. The wavelength maximum was found to be at 277 nm. The solubility for Prulifloxacin and Co-crystal was determined in water by dissolving 100 mg of drug and co-crystal in 100ml of water and making solution of 10ug/ml and it was determined by UV.
3. The differential scanning study was carried out using Metler Toledo differential scanning Calorimeter. Samples were placed in a aluminium crucible and the thermograms were recorded at heating rate of 10˚C/min in the range 30 to 300˚C.

FORMULATION OF IMMEDIATE RELEASE TABLET OF PRULIFLOXACIN

Compatibility study: to ensure the compatibility of drug with excipients the IR spectra for pure drug and prepared powder blend was obtained and analysed for principle peaks. The peaks obtain in powder obtained powder blends of formulation were almost identical to those obtained for pure drug revelling that there was no interaction between drug and polymers used in formulations.

Formulation of fast immediate released tablet was done in four steps.

First step: - preparation of co crystals was done by using different solvents in order to check the solubility of API and co crystal former which is developed by solution crystallization technique. Solvents use were dichloromethane, co-crystal former used were salicylic acid. Different ratios of co crystal were prepared and 1:0.5 ratio was selected, its solid state characterization was done by using melting point, FT-IR, DSC

Formulation of co-crystal- Different ratios of co crystals were prepared and 1:0.5 ratios was selected

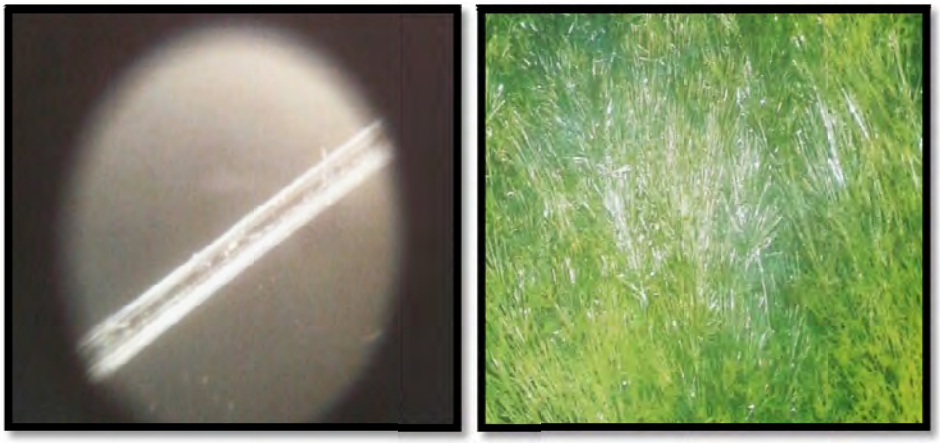


Fig No. 1 Co-crystals of Prulifloxacin

Second step: The tablets were prepared by using different super disintegrants and its combination in different to selecting best disintegrant for formulation of immediate release tablet

Third step: The tablets were prepared by wet granulation method.

Fourth step: Coating of prepared tablets

EVALUATION PARAMETER

PRECOMPRESSION PARAMETER [6, 7]:

BULK DENSITY (BD): 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,

$$\textbf{Bulk Density} = \frac{\textbf{Mass}}{\textbf{Bulk volume}}$$

TAPPED DENSITY (TD): 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,

$$\textbf{Tapped Density} = \frac{\textbf{Mass}}{\textbf{Tapped volume}}$$

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 and it is given as,

$$\boldsymbol{\theta} = \tan^{-1}\frac{\mathbf{h}}{\mathbf{r}}$$

Where,

- **θ** is the angle of repose
- **h** is the height in cm
- **r** is the radius.

Hausner ratio: it indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

$$\textbf{Hausner}'\textbf{s ratio} = \frac{\textbf{Bulk density}}{\textbf{Tapped density}}$$

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,

$$\mathbf{I} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \times \mathbf{100}$$

POST COMPRESSION PARAMETERS[6, 7]:

THICKNESS & DIAMETER: Thickness and diameter of tablets was determined using Vernier calliper. Five tablets from each batch were used, and average values were calculated.

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 min. The tablets were weighed again (W_{final}). The percentage friability was then calculated by:

$$\mathbf{F = \frac{Initial\ weight\ of\ tablet - Final\ weight\ of\ tablet}{Initial\ Weight\ of\ tablet} \times 100}$$

WEIGHT VARIATION TEST [8, 9]: 20 tablets of each formulation type were weighed individually using an electronic balance (0.01mg sensitivity). The average weight was calculated and individual tablet weight was compared with the average value and the deviation was recorded.

TEST FOR CONTENT UNIFORMITY OF ACTIVE INGREDIENT [8, 9]: drug content was determined by dissolving one tablet in 100 ml water and 5 ml aliquot were withdrawn and diluted into 10 ml and analyzed by using HPLC at 277 nm against blank prepared by using Placebo tablet.

DISINTEGRATION TEST: the test was carried out on the 6 tablets using the apparatus specified in USP, distilled water at 37˚+-2˚ was used as a disintegration media and the time in sec taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured in sec.

IN – VITRO DISSOLUTION TEST [10-15]: Transfer 6 tablets individually in six dissolution flasks containing 900ml of the medium that has been equilibrated to 37˚C+-0.5˚C. Collect the sample after the 5, 10,15,20,30 and 45 minutes. Sample was withdrawn from a zone midway between the surface of the medium and top of the rotating blade and not less than 1cm from the vessel wall and filter through 0.45u membrane filter.

Detection wavelength: 277 nm

ASSAY OF PRULIFLOXACIN TABLET:

Procedure: separately injects equal volumes (about 20ul) of the Standard preparation and the Assay preparation into the chromatograph, records the chromatograms, and measures the areas for the major peaks. Calculate the amount, in mg, of C14H21N3O2 sin the portion of Prulifloxacin taken by the formula:

(Peak area std/peak area test) x 24.9/50x 5/25x250/235.5x25/5x99.34/600x avg. wt of tabs.)

STABILITY STUDIES [16]: The stability studies of formulated tablets were carried out at 40˚C, RH 75% and at room temperature for one month. The effect of temperature and time on the physical characteristics of the tablet was evaluated for assessing the stability of the prepared formulations. The stability studies were carried out when the room temperature was 20˚ to 25˚ C. the different parameter that were studied are in vitro disintegration time, drug content and in vitro dissolution study.

CONCLUSION

Different ratios of co crystals were prepared and 1:0.5 ratios were selected. The immediate release tablet were prepared by using different super disintegrants such as crospovidone, crosscarmilose sodium.SSG(A) total nine formulations were prepared by addition of super disintegrant and evaluated for hardness,friability, weight variation, disintegrating time, and % in vitro drug release. Formulation containing croscarmilose sodium 1.8% produce rapid disintegration, so crosscarmilose sodium was selected for final formulation of rapid disintegrating tablet. F6 shows good results than other formulation and marketed formulation.

Table no. 1 Formulation of batches containing different disintegrant

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Prulifloxcin co crystals	600	600	600	600	600	600	600	600	600
Lactose monohydrate	375.3	368.7	362	375.3	368.7	362	375.3	368.7	362
Avicel-102	92	92	92	92	92	92	92	92	92
PVPK-30	12	12	12	12	12	12	12	12	12
SSG(0.6,1.2,1.8%)	6.7	13.3	20	-	-	-	-	-	-
Croscarmellose Sodium (0.6,1.2,1.8%)	-	-	-	6.7	13.3	20	-	-	-
Crosepovidone (0.6,1.2,1.8%)	-	-	-	-	-	-	6.7	13.3	20
Magnesium stearates	10	10	10	10	10	10	10	10	10
Aerosil	10	10	10	10	10	10	10	10	10
Total	1106	1106	1106	1106	1106	1106	1106	1106	1106

All quantities are taken in mg

Table No. 2 Evaluation of powder

Code	**Angle of repose**	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Hausner ratio**	**Carr's Index**
F1	27.528±0.235	0.561±0.032	0.634±0.043	1.130	11.51
F2	24.512±0.290	0.567±0.045	0.660±0.057	1.164	14.10
F3	27.210±0.352	0.574±0.058	0.652±0.083	1.135	11.96
F4	27.050±0.252	0.582±0.026	0.674±0.048	1.158	13.64
F5	24.625±0.374	0.575±0.048	0.680±0.061	1.182	15.44
F6	28.561±0.380	0.624±0.043	0.691±0.053	1.107	9.69
F7	24.840±0.972	0.607±0.057	0..667±0.063	1.098	8.99
F8	29.653±0.784	0.605±0.086	0.682±0.049	1.127	11.29
F9	28.462±0.850	0.611±0.048	0.679±0.057	1.111	10.01

Table No. 3 Evaluation of tablets prepared by different superdisintegrants

Code	Avg.wt.(mg)	Avg.Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegr-ation Time	(%)drug content
F1	1106±3.2494	10.266±0.1527	6.086±0.079	0.202±0.0302	4.33±1.03	98.89
F2	1106±1.6484	10.266±0.208	6.059±0.100	0.205±06500	2.51±1.02	98.42
F3	1106±1.7451	10.233±0.1553	6.038±0.0944	0.221±0.1105	2.29±0.65	97.82
F4	1106±1.9948	10.366±0.2516	6.020±0.0871	0.228±0.0480	1.07±0.84	99.22
F5	1106±1.5730	10.366±0.2081	6.013±0.0736	0.244±0.0966	0.55±0.35	98.77
F6	1106±3.9841	10.233±0.0577	6.047±0.1011	0.204±0.0853	0.48±0.53	100.83
F7	1106±3.1401	10.433±0.1527	6.012±0.1088	0.216±0.0861	1.26±0.56	99.65
F8	1106±2.1278	10.266±0.2081	6.035±0.1098	0.260±0.0547	1.03±0.73	99.01
F9	1106±2.1137	10.333±0.1527	6.045±0.089	0.181±0.0269	0.56±0.44	98.04

Table No. 4 Dissolution profile of all batches

Code	Percentage cumulative drug released (Mean ± S.D					
	Formulation code					
	F1	F2	F3	F4	F5	F6*
5	63.68±0.73	65.28±0.96	66.94±1.24	70.84±0.80	74.28±1.28	80.23±0.51
10	70.66±0.46	74.96±1.12	78.04±0.42	81.21±1.06	82.66±1.56	86.21±1.25
15	77.80±0.29	79.93±0.22	81.98±0.80	82.99±1.49	90.73±0.78	92.88±0.46
20	80.62±0.95	84.91±0.49	86.81±1.57	90.51±0.77	92.91±0.39	96.51±2.51
30	89.43±1.31	92.91±1.18	93.32±1.49	94.38±0.93	96.91±2.65	100.38±1.2
45	95.60±0.65	96.89±0.80	97.99±0.47	96.28±1.25	98.89±0.85	100.68±0.8

Code	Percentage cumulative drug released (Mean ± S.D		
	Formulation code		
	F7	F8	F9
5	62.28 ± 0.64	70.73 ±0.79	74.41 ±0.56
10	67.66 ±1.46	76.85 ±1.21	80.04 ±1.38
15	74.73 ±1.87	80.98 ±0.68	86.92 ±0.33
20	83.91 ±0.48	86.30 ±1.26	92.64 ±1.61
30	89.91 ±2.39	94.17 ±2.34	96.37 ±1.17
45	94.89 ±0.96	98.84 ±1.10	99.42 ±1.35

Table No. 5 Calculation for assay

Claims	Potency	Std. wt.	Avg.wt.	Spl wt	Std.area	Test area
600mg	99.34%	24.9 mg	1131.65mg	235.5mg	11521912	11451673

$$\text{Assay} = \frac{11521912 \times 24.9 \times 5 \times 250 \times 25 \times 90.34 \times 1131.65}{11451673 \times 50 \times 25 \times 235.5 \times 5 \times 600} = 99.6595\%$$

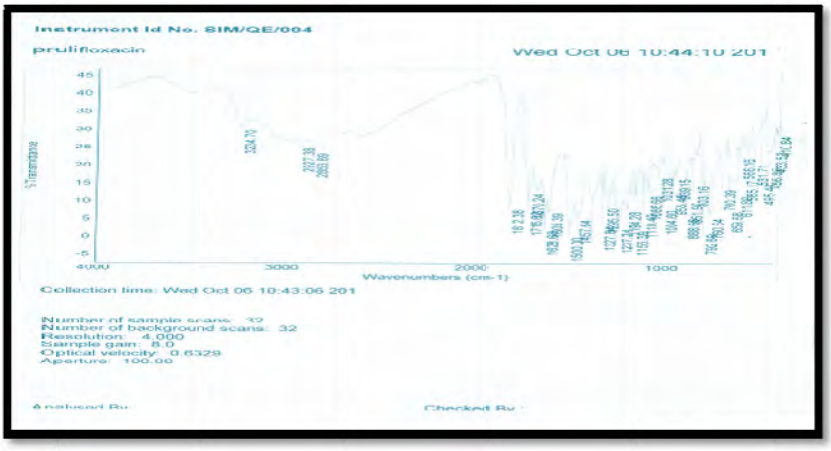


Fig. No. 2 F.T.I.R. Spectra of Prulifloxacin pure drug

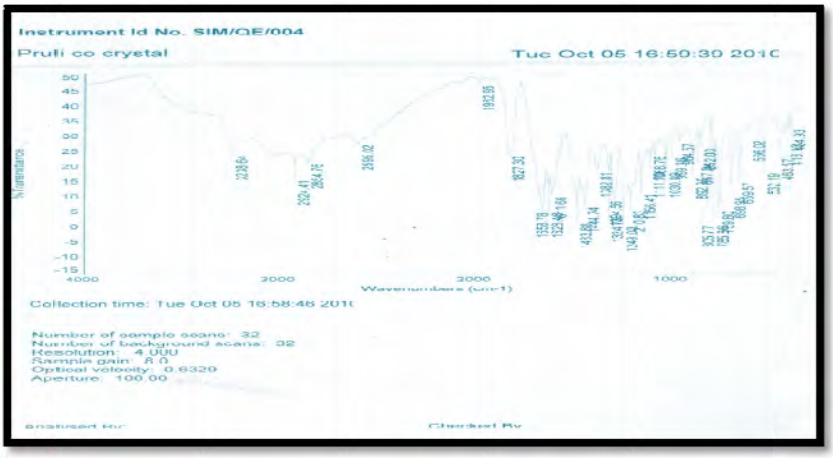


Figure No. 3 F.T.I.R. Spectra of Prulifloxacin co-crystal + Excipients

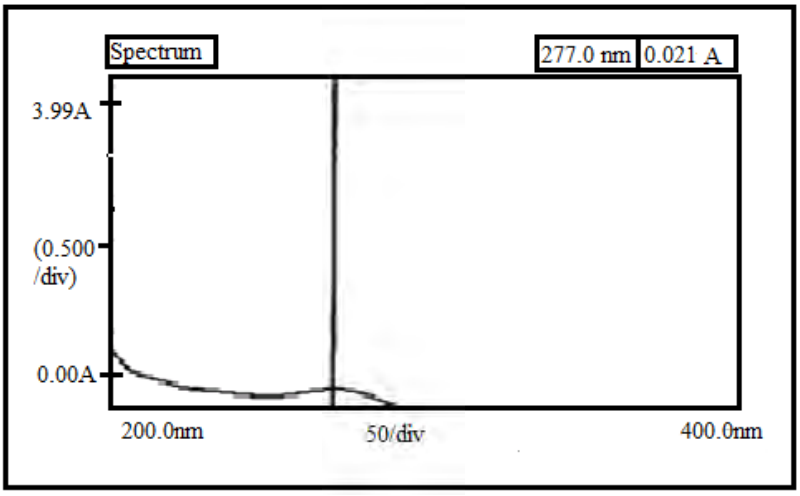
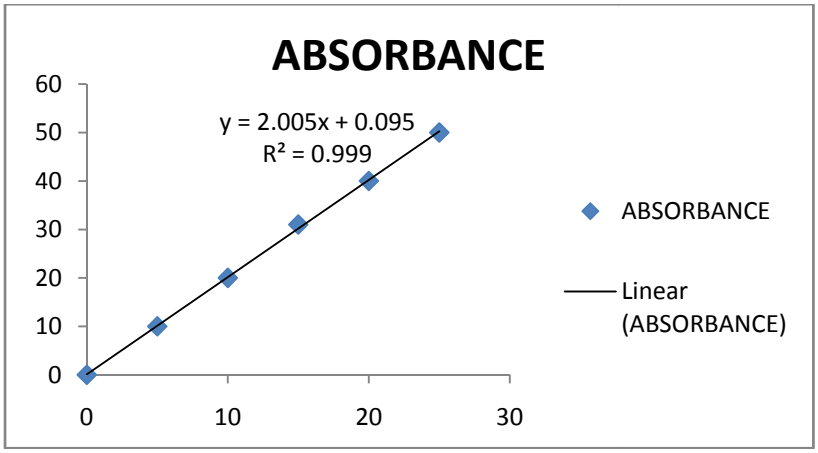


Figure No. 4 Calibration curve of Prulifloxacin



Calibration curve of Prulifloxacin

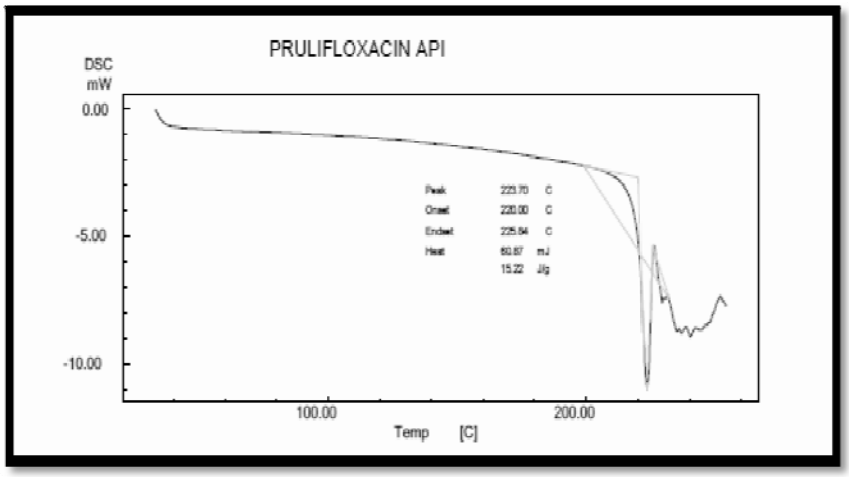


Figure No. 5 DSC for Prulifloxacin

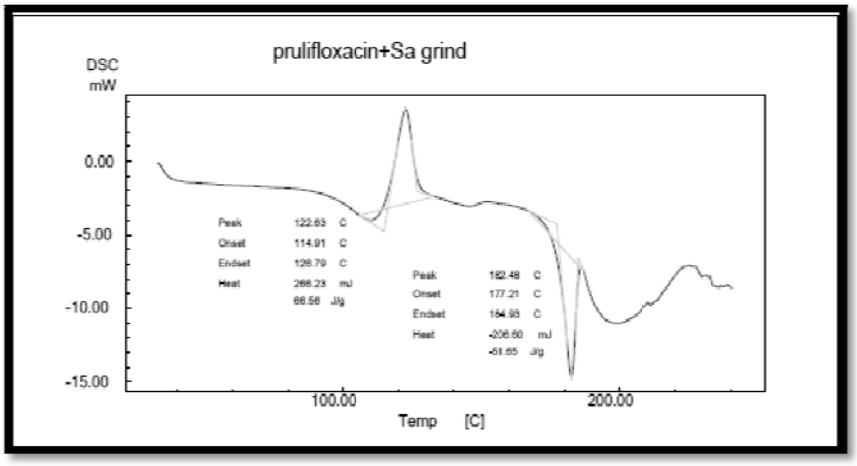


Figure No. 6 DSC for prulifloxacin co-crystal

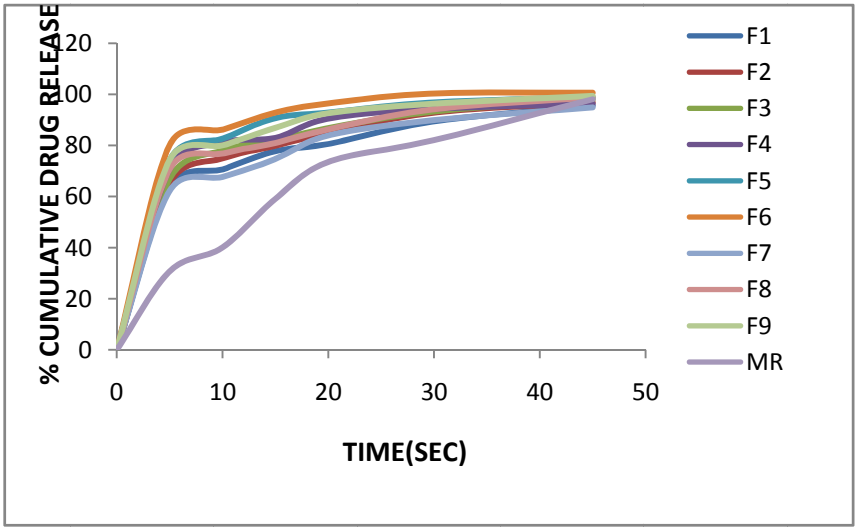


Figure No. 7 Dissolution profile of all batches and marketed preparation

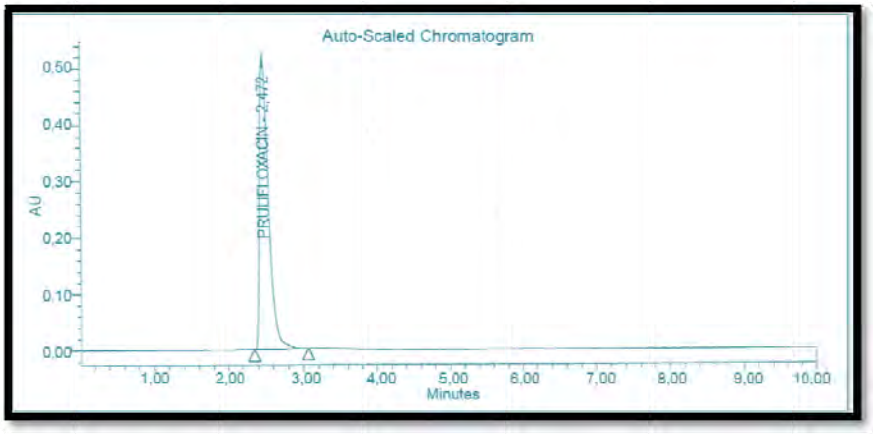


Figure No. 8 HPLC Chromatogram for standard Prulifloxacin

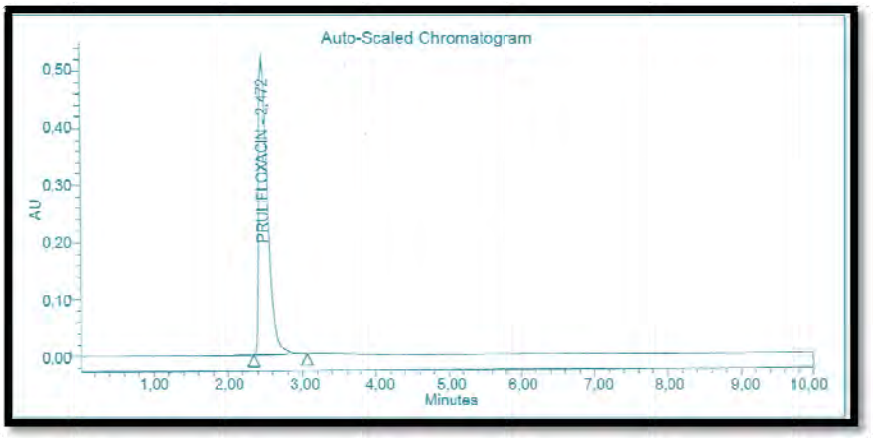


Figure No. 9 HPLC Chromatogram prulifloxacin Co crystal tablet

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