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FORMULATION, EVALUATION AND OPTIMISATION OF RAPID ONSET CEFPODOXIME PROXETIL USING MUSA PARADISIACA

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ABSTRACT

The objective of the present study was to develop the fast dissolving tablets of Cefpodoxime proxetil to reduce the drug releasing time and to provide faster onset of action to relieve pain. This would be advantageous as the conventional solid dosage forms are often associated with a faster disintegrating time. In this study, the fast dissolving tablets containing Musa paradisiaca (banana powder) provided quicker disintegration of the tablets there by releasing the drug immediately. The preformulation studies using FTIR spectroscopy had revealed that there is no incompatibility between the drug and excipients. Among the different batches prepared, it was found that the Formulation2 containing, Cefpodoxime proxetil 50mg, Musa paradisiaca powder 100mg and lactose 25mg released all the drug content in 8 minutes and hence was proved as the best formulation. Suitability for the high compression and good strength were observed when the powder was physically evaluated. The disintegration/dissolution studies confirmed the strength of Musa paradisiaca powder as a super disintegrant when compared to crospovidone and microcrystalline cellulose.

KEYWORDS : *Cefpodoxime proxetil, Musa Paradisiaca, Crospovidone, Micro crystalline cellulose, Fast Dissolving Tablets*.

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INTRODUCTION

Cefpodoxime proxetil (CP) has been rendered as an excellent choice for 'first line' or blind therapy', due to the broad spectrum of activity of third generation cephalosporin against gram-positive and gram-negative bacterial infections, especially in which penicillin-resistant organisms may be present[1]. The studies demonstrate the cefpodoxime activity as excellent, against a wide range of pathogens such as Respiratory pathogens, Enterobacteriaceae and Gram-positive cocci[2,3,4,5]. Due to the presence of aminothiazolyl group, cefpodoxime may share enhanced activity,whilethe β- lactamase stability is seen with the use of newer agents[5].

Cefpodoxime proxetil (CP) is a prodrug, third generation cephem type broad spectrum antibiotic administered orally. CP is a slightly basic compound, non-crystalline and possesses an asymmetric carbon atom in the ester group and has been supplied as a racemic mixture of R and S isomer[5,6,7,8]. It has also been known to exhibit a pH dependent solubility, with enhanced solubility in acidic conditions and declined solubility in less acidic conditions. The mechanism of antibacterial action of cefpodoxime is mainly through the inhibition of bacterial cell wall synthesis. This is by acylation of membrane bound Trans peptidase enzymes, which prevents the cross linkage of peptidoglycan chains that is necessary for bacterial cell wall strength and rigidity. CP is absorbed orally and hydrolysed rapidly by non-specific esterases in the gastro-intestinal wall to cefpodoxime, the active acid[9, 10, 11]. During the low gastric activity, the absorption is decreased. After oral administration, a single dose of 100 to 400mg of cefpodoxime proxetil the maximum plasma concentration C_{max} obtained is 1.4 to 3.9mcg/L. The bioavailability is about 50%. The time taken to reach maximum concentration T_{max} is about 2 to 3 hours. Of about29% to 33% of the absorbed dose is excreted unchanged in the urine in 12hrs.The elimination ($t_{1/2}$) is 2.09 to 2.84hrs[12,13]. To enhance the rapidity of onset of action and the bioavailability, a fast dissolving formulation of Cefpodoxime proxetil has to be developed.

The main objective of the present investigation was to develop the fast dissolving drug delivery system of Cefpodoxime proxetil using Musa paradisiaca powder[14,15] and crospovidone. Varying ratios of drug and polymer with Musa paradisiaca were selected and explored. The tablets prepared were evaluated for different physicochemical parameters such as appearance, weight variation, thickness, hardness, friability, drug content and in vitro release.

MATERIALS AND METHODS

Cefpodoxime proxetil was a gift sample obtained from Sashan Pharmaceutical Pvt. Ltd, Coimbatore. Crospovidone was purchased from Colorcon Asia Pvt Ltd, India. Micro crystalline cellulose was purchased from FMC Biopolymers, USA. Talc was purchased from Luzenac, France. 0.45µ (Millipore) filter was obtained from Millipore, USA. Magnesium stearate was purchased from Ferro Industrial Chemicals, USA. Musa paradisiaca powder was prepared in the laboratory using drying and mixing methods. Lactose was purchased from S. D fine chemicals, India. All other solvents and reagents were of analytical grade.

Formulation of Fast Dissolving Tablets

Fast dissolving tablets of Cefpodoxime proxetil were prepared using various proportions of Musa paradisiaca powder and Crospovidone as the polymer. The tablets were manufactured by direct compression procedure. The lubricated granules were directly compressed using 9mm flat faced round (FFR) punch. Three batches were prepared for each formulation and from each batch 500 tablets were compressed for the characterisation study. The formulae and physical characteristics of the prepared tablets were shown in the tables 1, 2, 3.

Preparation of the tablets using Direct Compression Method

The drug, Musa paradisiaca powder, polymer and all other excipients were sifted through 425µ sieve (ASTM mesh no 40) and mixed uniformly. The dry mix blend was then pre-lubricated with respective excipients and lubricated with magnesium stearate. The lubricated granules

were directly compressed on 16 station tablet compression machine using respective punches (Cadmach Machinery Co, Ahmadabad, India).

Preparation of matrix tablets using wet granulation method

The drug, polymer and other excipients were shifted through 425µ sieve (ASTM mesh no 40) and mixed uniformly. The dry mix blend was then granulated with respective granulation fluid. The wet granules were dried at 60^0C until the complete evaporation of granulation fluid from the granules. The dried granules were again sifted through ASTM mesh no. 30. The dried and sifted granules were then pre lubricated with respective excipients and then lubricated with magnesium stearate. The lubricated granules were compressed on 10 station tablet compression machine using respective punches (Cadmach Machinery Co, Ahmadabad, India).

Table 1. Compositions of formulations (F1 – F6)

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Drug	50mg	50mg	50mg	50mg	50mg	50mg
2	Musa paradisiaca	25mg	50mg	75mg	100mg	125mg	150mg
3	Lactose	25mg	25mg	25mg	25mg	25mg	25mg
4	Talc	2%	2%	2%	2%	2%	2%
5	Magnesium stearate	2%	2%	2%	2%	2%	2%

Table.2. Compositions of formulations (F7 – F10)

S.No	Ingredients	F7	F8	F9	F10
1	Drug	50mg	50mg	50mg	50mg
2	Crospovidone	75mg	100mg	-	-
3	MCC	-	-	75mg	100mg
4	Lactose	25mg	25mg	25mg	25mg
5	Talc	2%	2%	2%	2%
6	Mg. Stearate	2%	2%	2%	2%

Evaluation of the Tablets

The prepared tablets were evaluated for hardness, thickness, friability, drug content and in vitro release studies. The hardness of the tablet was determined for 10 tablets using a Monsanto hardness tester (MHT-20, Campbell Electronics, Mumbai, India). The tablet to be tested is placed between the spindle and anvil and pressure applied by turning the screw knob just to hold the tablet in position. The reading of the indicator on the scale is adjusted to zero. The pressure is applied until the tablet breaks. The reading was noted. In this study, for each formulation the hardness of 6 tablets was evaluated.

The weight variation was determined by taking 20 tablets using an electronic balance (type ER 182A, Mettler Toledo). In weight variation test twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight.

The friability of the tablets was determined by testing 10 tablets in a Friability tester (FTA-20 Campbell Electronics) for 300 revolutions at 25 rpm. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test. For the determination of drug content, the prepared matrix tablets were divided in triplicate. For each batch, 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken and suitably dissolved under sonication (power sonic 505, HWASHIN technology Co) in pH 6.8 phosphate buffer and filtered through 0.45 µ (Millipore) filters. The samples were analysed by UV visible spectrophotometer at 285nm after making appropriate dilutions The in vitro dissolution studies were performed up to 14 h using USP type-2dissolution apparatus (paddle type, LABINDIA,DISSO -2000, Mumbai, India)at 100 rpm. The dissolution medium consisted of phosphate buffer pH 6.8(900ml), maintained at 37^{o}C. An aliquot (5ml) was withdrawn at specific time intervals and filtered through 0.45 µ (Millipore) filter. After appropriate dilutions, the samples were analysed by UV visible spectrophotometer at 285nm and cumulative percentage of the drug release was calculated. The mean of6 tablets from 3 different batches were used in data analysis.

Fourier Transform Infrared Radiation measurement

The FT-IR spectrums of pure drug, initial formulation and stability samples of matrix tablets were determined. FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4400 cm^{-1} and 4 cm^{-1} resolution. The results were the means of 6determinations. A quantity equivalent to 2 mg of pure drug was used for the study.

RESULTS AND DISCUSSION

Physical evaluation of the powder blends:

Table 3. Physical characteristics of powder blends

S. No	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Bulk density (g/ml)	0.5524	0.5541	0.5537	0.5514	0.5578	0.5564	0.5489	0.5595	0.5490	0.5571
2	Tapped density(g/ml)	0.6478	0.6484	0.6458	0.6487	0.6452	0.6458	0.6423	0.6489	0.6578	0.6548
3	Hausner ratio	1.107	1.108	1.108	1.111	1.118	1.102	1.107	1.112	1.101	1.105
4	Carr's index (%)	9.55	9.84	9.81	9.86	9.88	9.81	9.84	9.88	9.84	9.85
5	Angle of repose (θ)	22^{0}.43'	22^{o},58'	23^{o},52'	23^{o},52'	22^{o},58'	22^{0}.43'	23^{o},52'	22^{o},58'	23^{o},52'	23^{o},52'

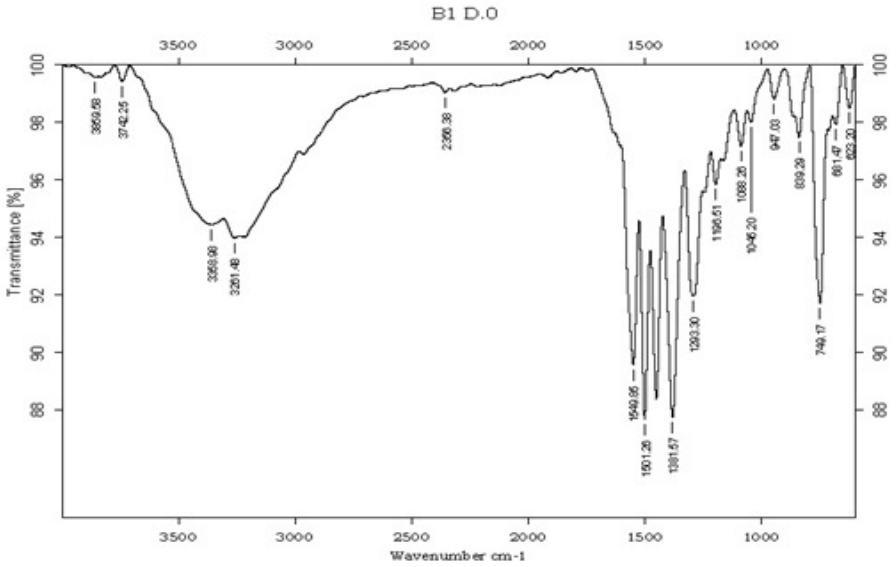

Figure 1. FTIR Spectra of Cefpodoxime proxetil

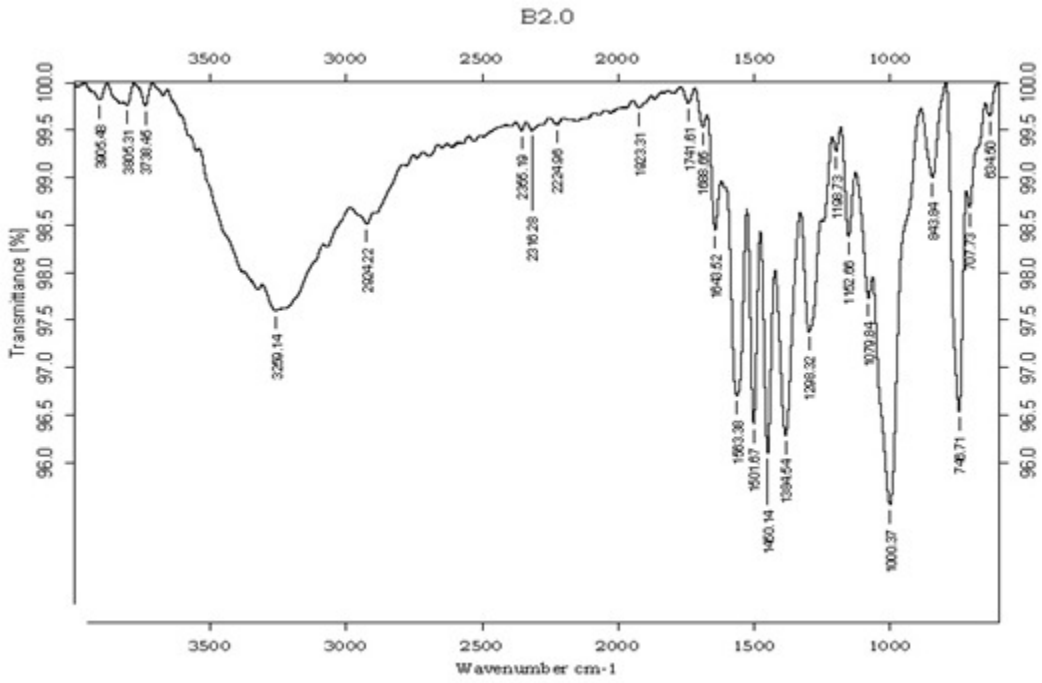

Figure 2. FTIR Spectra of Banana powder

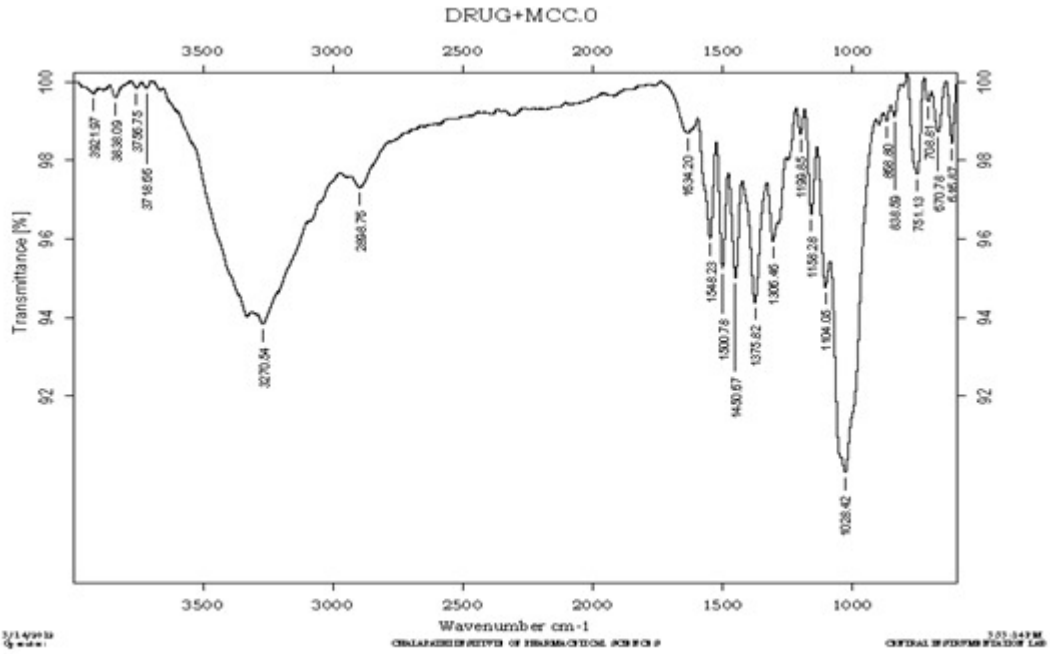

Figure 3. FTIR Spectra of Drug with MCC

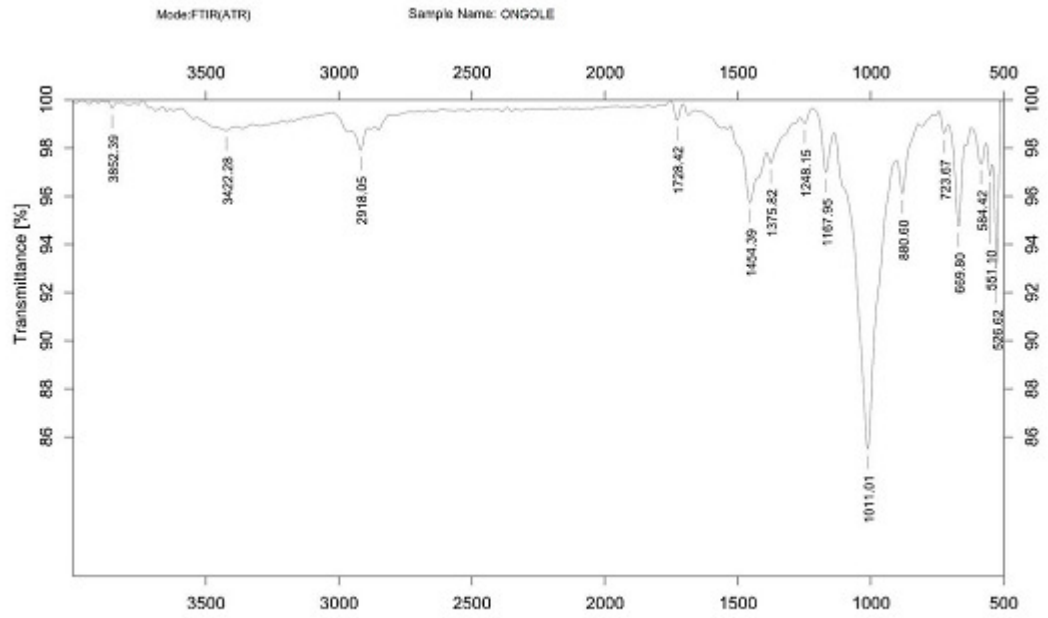

Figure 4. FTIR Spectra of Drug with banana powder

Preformulation Studies:

Table 4. Physical Characterisation of Formulations F1 – F10

S.No	Formulation	Thickness (mm)	Hardness (Kg/cm^2)	Friability	Wt. variation
1	F1	2.74±0.05	2.66±024	Pass	Pass
2	F2	2.84±0.04	2.62±0.16	Pass	Pass
3	F3	2.80±0.04	2.66±0.20	Pass	Pass
4	F4	2.83±0.05	2.84±0.18	Pass	Pass

5	F5	2.83±0.06	2.84±0.14	Pass	Pass
6	F6	2.76±0.06	2.80±0.17	Fail	Pass
7	F7	2.81±0.04	2.80±0.16	Pass	Pass
8	F8	2.84±0.04	2.72±0.23	Pass	Pass
9	F9	2.83±0.07	2.76±0.18	Pass	Pass
10	F10	2.85±0.04	2.74±0.15	Pass	Pass

Table 5. Dissolution data of Formulations F1 – F10

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	8.199	15.335	9.578	8.437	9.62	7.724	10.578	8.437	10.578	7.724
2	29.614	25.579	30.282	28.901	30.33	30.090	31.282	30.090	20.817	29.376
3	45.583	46.062	44.587	45.582	45.585	45.583	45.587	45.584	39.868	45.582
4	63.710	69.66	63.665	63.233	64.426	62.996	64.665	64.186	51.090	63.233
5	83.283	80.202	82.003	83.045	83.762	83.758	84.003	83.760	68.272	83.758
6	86.934	89.312	87.841	88.360	87.888	88.124	88.841	87.412	78.563	87.648
7	89.138	91.523	88.856	90.091	88.903	89.853	89.856	90.091	89.330	90.091
8	91.80	96.806	94.137	95.372	93.945	95.134	95.137	95.373	94.379	95.610

Table 6. Disintegration time data of Formulations F1 – F10

S.No	Formulations	Disintegration time (min)
1	F1	08±2
2	F2	08±1
3	F3	07±2
4	F4	06±3
5	F5	08±1
6	F6	08±2
7	F7	06±3
8	F8	06±2
9	F9	06±1
10	F10	05±2

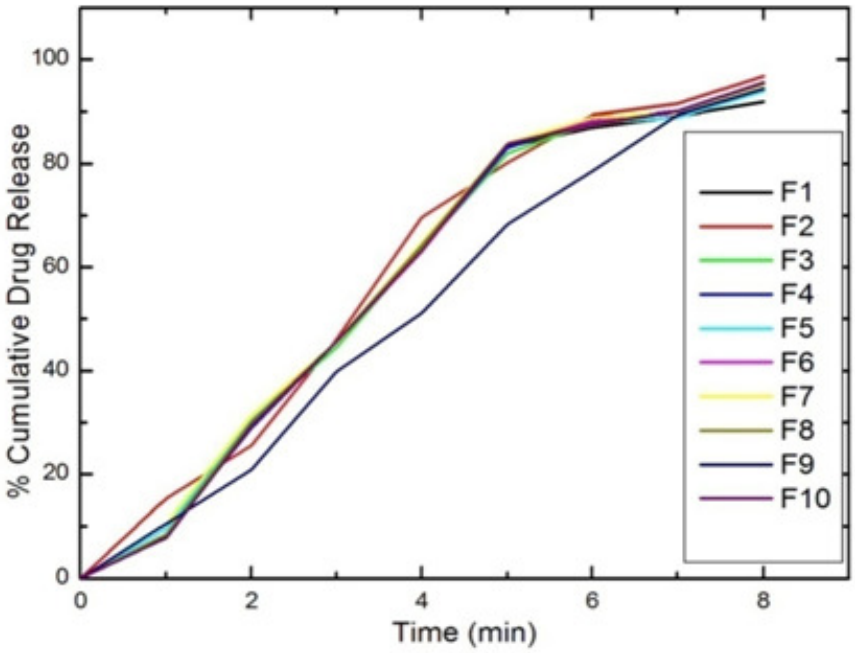

Figure 5. Dissolution profiles of Formulations F1 – F10

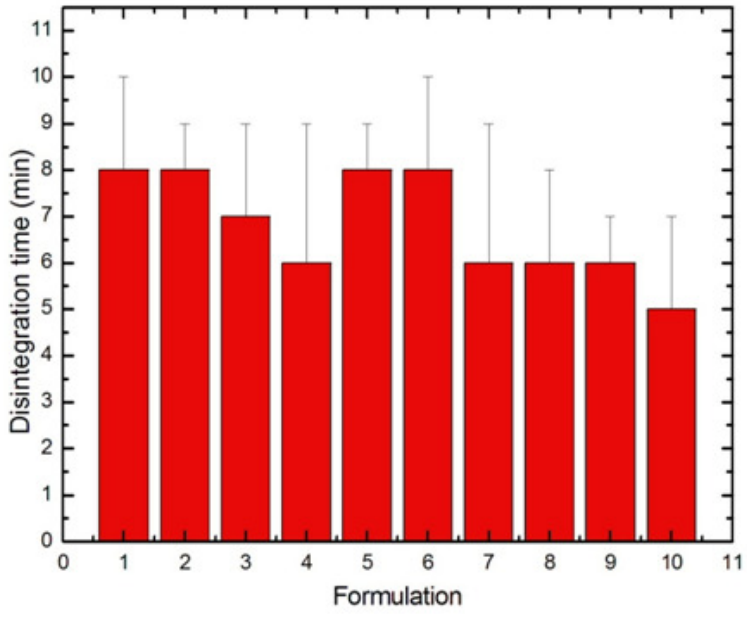

Figure 6. Disintegration time profile of Formulations F1 – F10

The prepared banana powder and the drug was blended using granulation method and then characterised physically. Table.3 shows the results attained after evaluation of different physical characteristics of the powder blend.

The physical evaluation revealed that the powder blend has an optimum strength and good angle of repose such that all the formulations were suitable for compression at high speed.After the physical evaluation of the powder blend, the lubricated granules were compressed on 10 station tablet compression machine using respective punches.Later preformulation studies were performed by using FTIR spectroscopy method. The IR spectra of the pure drug, Fig. 1 and banana powder, Fig. 2 were compared with IR spectra Fig. 3 & Fig. 4 of the powder blend of the various formulations.The absence of appearance or

disappearance of characteristic peaks in the spectra confirms that there was no incompatibility between the drug and the banana powder taken for the study.

The prepared formulations had undergone different physical tests. Table.4 shows the results attained after performing thickness, hardness, friability and weight variation tests.A comparative study has been performed among all the formulations, to choose a better formulation and to understand the effect of different disintegrant's used. Starting with the formulation1 (F1) though has shown the higher disintergration time, found to be having the lowest thickness and lowest dissolution profile with only 91.180% drug release. Formulation3 (F3) found to be not very competitive with disintegration time, and lower dissolution profile with 94.137% drug release. Formulation4, 5 (F4, F5) having a greater hardness, has shown lower dissolution profile with only 95.372% & 93.945% drug release respectively. Though, formulation6 (F6) has shown effective disintegration, it failed to show an optimum range in drug release studies. Also in formulation6, the friability test has been failed (Table 4), which has been assumed to be due to the content (Table 1) of disintegrant used. The other formulations F7, F8 and F9, were not very effective and uncompetitive when compared to the other formulations. Formulation10 (F10) found to be lower compared to Formulation 2 (F2), in drug release studies. Among all the formulations explored, dissolution profile with 96.806% drug release and higher disintegration time (Table.5 & Table. 6), formulation2 (F2) (Fig. 5, Fig. 6) has been proved to be an optimum and the best formulation. It has also shown greater thickness and friability, and has been considered as the best formulation among all the other formulations.

Among the different disintegrant's explored in this study, micro crystalline cellulose (MCC) and crospovidone were found to be effective only to a certain extent. Their efficiency was restricted only to the physicochemical parameters and disintegration of the tablets. The novel disintegrant explored in this study was Musa paradisiaca (banana powder) has proved to be an effective, and revealed synergistic results in physicochemical parameters and disintegration along with an excellent drug release profile.

CONCLUSION

Cefpodoxime proxetil (CP) has been rendered as excellent choice for 'first line' or blind therapy', due to the broad spectrum of activity of third generation cephalosporin against gram-positive and gram-negative bacterial infections. Cefpodoxime proxetil (CP) is a prodrug, third generation cephem type broad spectrum antibiotic administered orally. Hence an attempt has been made for preparation of fast dissolving tablets of, Cefpodoxime proxetil with an aim of fast disintegration. The fast dissolving tablet would be having *Musa paradisiaca* powder to provide quick disintegration and for immediate release of drug.

Preformulation studies using FTIR spectroscopy was done to reveal that there was no incompatibility between drug and the *Musa paradisiaca* powder. The fast dissolving tablets were formulated with 50 mg drug loading and banana powder is used as super disintegrating agent. It was found that the formulation 2 (Cefpodoxime proxetil 50 mg, *Musa paradisiaca* powder 100mg, lactose 25 mg.) released all its drug content within 8 minutes and hence selected as the best formulation. The physical evaluation of the powder demonstrated that are of good strength and suitable for high speed compression.

The disintegration/ dissolution rate were compared with the super disintegrating agents like crospovidone and micro crystalline cellulose by performing different formulations. The drug release studies revealed the Musa paradisiaca (banana powder) as good disintegrating agent compared to crospovidone and micro crystalline cellulose.

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