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Formulation and Evaluation Of Dispersible Tablets of Cefpodoxime Proxetil

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ABSTRACT

The demand of solid oral drug delivery systems has been growing during the last decade especially for geriatric and pediatric patients because of difficulties in administration through other routes. Hence the present research work is directed towards development of dispersible tablets of cefpodoxime proxetil using direct compression attributed to rapid disintegration of dispersible tablet in water forming a stabilized dispersion.

These tablets were prepared by using crospovidone, sodium starch glycolate and croscarmellose sodium as superdisintegrants in different concentration. Total nine formulations were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and in-vitro drug release (all tests were performed as mentioned in the Pharmacopoeia IP or USP). The stability studies were performed as per ICH guidelines. Stability study of final batch showed no significant changes in tablet properties.

F9 formulation was found to be superior as it showed better results than other formulations disintegration time, percentage drug release and dispersion time were 26 seconds, 98.83% and 31.1 seconds respectively. Showing better disintegration time and drug release than other formulation

Key-words:

Cefpodoxime Proxetil, Crospovidone, Dispersible tablet, direct compression.

INTRODUCTION

Cefpodoxime Proxetil is third generation, broad-spectrum cephalosporin antibiotic mainly used in treatment of respiratory, urinary, skin and soft tissue infections caused by gram positive and gram negative bacteria.[1] Effective average daily dosages of this antibiotic is typically quite high thus conventional tablet dosage form is inconvenient to swallow by the very young or the elderly. It has been reported that dysphasia is common among all age groups of patients but is more specific to pediatrics, geriatrics along with institutionalized patients and patients with nausea, vomiting and motion sickness complications, pediatric and geriatric patients may encounter inconvenience in swallowing it.[2,3] Cefpodoxime Proxetil is a molecule which has a very low solubility in water. Therefore oral bioavailability of the tablet form is 50% less than Cefpodoxime given intravenously. Alternatively the use of reliable and user friendly water dispersible forms are suggested.[4]

Over the past one decade, there has been an enhanced demand for more patient friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing. Since the development cost of new drug molecule is very high, efforts are now being made to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy, bioavailability together with reduced dosing frequency, and the production of more cost effective dosage forms. To fulfill these medical needs, pharmaceutical technologies have developed a novel oral dosage form known as dispersible tablet, which disintegrate rapidly in small amount of water, usually in a matter of few seconds. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms. Dispersible tablets offer advantage for patients who have difficulty in swallowing. Dispersible tablets with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

Materials and methods

Cefpodoxime proxetil provided as a gift sample by Covalent Laboratories Pvt Ltd. Superdisintegrants (Crospovidone, Croscarmellose Sodium and Sodium starch glycolate) were purchased from Yarrow chemical, Mumbai. All other excipients and chemicals used were of suitable analytical grade.

Formulation of dispersible tablets of Cefpodoxime Proxetil:

The tablets of cefpodoxime proxetil were prepared by using direct compression technique. Accurate amount of the cefpodoxime proxetil sifted through #30 and all additives sifted through sieve #40 were homogeneously blended in geometric dilutions. Magnesium stearate and sodium lauryl sulphate were taken previously sifted through #60 and added as a lubricant to the blend in the planetary mixer. These

blended mixtures were compressed by using tablet compression machine having 11 mm, FFBE (flat face bevel edges) punch as being plane on both the sides. A weight of 380mg was maintained for all the tablets. Compositions of each formulation are given in table No. 1

Table No. 1: Formulation of dispersible tablets of Cefpodoxime Proxetil

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
CEFPODOXIME PROXETIL	70	70	70	70	70	70	70	70	70
LACTOSE	78	73	38	78	73	38	78	73	38
MAIZE STARCH	60	50	70	60	50	70	60	50	70
SSG	15	20	25	-	-	-	-	-	-
CROSCARMELLOSE	-	-	-	15	20	25	-	-	-
CROSSPOVIDONE	-	-	-	-	-	-	15	20	25
MCC 200	100	110	120	100	110	120	100	110	120
SUCRALOSE	23	23	23	23	23	23	23	23	23
SODIUM CHLORIDE	4	4	4	4	4	4	4	4	4
ORANGE FLAVOUR	12	12	12	12	12	12	12	12	12
AEROSIL	9	9	9	9	9	9	9	9	9
SLS	5	5	5	5	5	5	5	5	5
MG. STEARATE	4	4	4	4	4	4	4	4	4
TOTAL WEIGHT	380	380	380	380	380	380	380	380	380

Evaluation of tablets for Precompression parameters:

Pre-compression parameters:[5,6]

Formulations ready for compression containing drug and various excipients were subjected for pre-compression parameters to study the flow properties of granules (angle of repose, mean bulk density, mean tapped density, carr's index, hausner's ratio).

Post- compression parameters

Physical Characterization of tablets:

Twenty tablets were randomly selected from the prepared formulations and examined for shape, thickness & diameter.

Hardness: [6]

Ten tablets were randomly selected from each formulation and hardness of the same was determined by using Monsanto hardness tester. Average value was calculated and was expressed in Kilogram per centimeter square (kg/cm^2).

Friability: [6]

Friability test is performed according to USP specifications using Roche friabilator. Since the tablet weight (380mg) was always less than 650 mg, a random sample of whole tablets corresponding to 6.5 g was dedusted, accurately weighed, and placed in the drum of a Roche Friability tester. Drum was rotated 100 times and tablets were removed, dedusted, and accurately weighed. The percentage friability was calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

% Friability of tablets less than 1 % is considered acceptable.

Weight variation: [5]

As per USP specifications to perform test for uniformity of weight twenty tablets from each formulation were selected randomly and their average weights were calculated. Percentage weight differences were calculated and checked with USP specifications.

Drug content uniformity: [7]

Twenty tablets from each formulation were weigh and crushed in a mortar. From that 10mg of tablet powder was accurately weighed and transferred in 100ml of 0.1N methanolic hydrochloric acid and was sonicated for 180 seconds and filtered through whatmann filter paper No. 40. The 1ml of this filtrate was further diluted with 100ml of 0.1N methanolic hydrochloric acid to get concentration of 10µg/ml. Absorbance measure at 262nm. By using slope of standard calibration curve the amount of Cefpodoxime Proxetil was calculated.

Wetting Time: [8,9]

A piece of tissue paper folded twice was kept in petri dish (internal diameter 5.5 cm) containing 10 ml of distilled water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develope a red colour on the upper surface of the tablet was recorded as wetting time.

Water Absorption Ratio: [8,9]

A piece of tissue paper folded twice was placed in a small Petri dish (5 cm diameter) containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then weighed and the water absorption ratio 'R' was determined by using following equation.

$$R = \frac{W_b - W_a}{W_a} \times 100$$

Where,
W_a= weight of tablet before water absorption
W_b = weight of tablet after water absorption.

***In-vitro* Disintegration Study:** [7,10]

The in-vitro disintegration test for prepared tablets was carried out using USP Disintegration Test Apparatus-II. Six tablets were placed individually in each tube of disintegration test apparatus and Discs were placed over each tablet. Distilled water was used as the medium which is maintained at 37 ± 2°C and the time taken for each tablet to disintegrate completely was recorded.

***In-vitro* Drug release studies:** [11, 12]

In-vitro dissolution study was carried out using USP XXII dissolution test apparatus type II. The dissolution medium used was 900 ml of 0.1N HCl solution, which was maintained at 37°C±1°C. The paddle speed was kept at 75 rpm throughout the study. A 5ml of sample was withdrawn at 30 min interval and diluted adequately. The samples was analyzed spectrophotometrically at 262 nm using 0.1N HCl as blank. The raw dissolution data was analyzed for calculating the total amount of drug released at the end of 30 minutes.

In-vitro dispersion time:[13]

Tablet was added to 10 ml of distilled water at 37±0.5ºC. Time required for complete dispersion of tablet was measured.

Table No. 2: Dissolution parameters

Parameter	Value
Dissolution medium	900 ml of 0.1N HCl
Temperature	37°C ± 1°C
RPM	75
Tablet taken	One tablet (Known drug content).
Volume withdrawn	5ml
Volume made up to	25 ml
λmax	262 nm
Dilution factor	5

Stability studies:[14]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, retest periods and shelf lives to be established. In the present study, stability studies were carried out at 40 ± 2°C/ 75 ± 5 % RH. Each tablet was individually weighed and packed in an aluminum foil and placed at above specified conditioned in a stability chamber for One month.

Results and discussions

Pre- compression parameters:

Precompression studies of all formulation showed acceptable flow properties with respect to angle of repose and Housner's Ratio. The values of Carr's Index showed that satisfactory packing ability of the formulations. There was better compressibility observed with Crospovidone in comparison to sodium starch glycolate and Croscarmellose sodium due to its smaller particle size**.** The results of precompression parameters analysis were given in table No.3.

Table No.3: Pre-compression parameters of all the formulations

F. No.	Bulk Density (gm/cm³) (n=3)Mean±SD	Tapped density (gm/cm³) (n=3) Mean±SD	Carr's Index (%) (n=3) Mean±SD	Hausner Ratio (n=3)Mean±SD	Angle of repose (n=3) Mean±SD
F1	0.6±0.002	0.46±0.005	23.33±0.02	1.30±0.014	31º ± 0.69
F2	0.59±0.003	0.46±0.003	22.03±0.06	1.28±0.015	29º± 1.13
F3	0.65±0.002	0.51±0.002	21.53±0.18	1.27±0.007	29º± 0.65
F4	0.59±0.002	0.45±0.018	23.72±0.07	1.31±0.007	29º ±0.42
F5	0.58±0.018	0.47±0.005	18.96±0.02	1.23±0.013	29º± 0.88
F6	0.62±0.003	0.51±0.003	17.74±0.04	1.21±0.007	30º± 0.67
F7	0.64±0.002	0.46±0.002	22.5±0.18	1.29±0.011	30º± 0.66
F8	0.59±0.019	0.47±0.003	20.33±0.04	1.25±0.006	28º± 0.79
F9	0.61±0.002	0.49±0.005	18.33±0.07	1.22±0.013	28º± 0.77

Post-compression parameters

Physical Characterization of tablets:

Physical characterization of all formulations showed that prepared tablets were flat, circular shape and off-white in color having thickness ranged from 3.70± 0.01 mm to 4.10± 0.011 mm. The standard deviation values indicated that all the formulations were within the Indian Pharmacopeial range (± 0.2 mm). The results of thickness for tablets were shown in Table No.4.

Hardness: -

The hardness of all the tablets prepared by direct compression methods was found to be within 3.59±0.21 kg/cm2 to 4.25±0.12kg/cm2 which is acceptable. The mean hardness test results are tabulated in Table No.4.

Friability test: -

The friability of all the tablets prepared by direct compression methods using co-grinding process was within 0.205% to 0.48%. The values were found to be within the limit (<1%) in all designed formulations.

Thus tablets possess good mechanical strength & comply with the pharmacopoeial standard. The results of friability for tablets were shown in Table No.4.

Weight variation test: -

The weight variation of all the tablets was found between 378.95±3.50mg to 382.1±1.19mg which is within pharmacopeial limit. Thus was acceptable.

Drug content:

As per Indian Pharmacopoeial specifications, the drug content should in range of not less than 85% and not more than 115%. Based on results of test for content uniformity, all formulations were passed the test.

Table No.4: Post-Compression Parameters of All Formulations

Formulation code	Hardness (Kg/cm ^{2})	Thickness\ (mm) (n=10)	Friability (%)	Weight Variation (n=20)		Content of drug uniformity *(%)
				Mg	%	
F1	3.59±0.21	4.10± 0.01	0.360	382.1±1.19	0.55	97.526±2.38
F2	4.25±0.12	4.10± 0.01	0.205	380.6±2.08	0.15	98.697±2.54
F3	3.81±0.1	4.10± 0.01	0.335	381.55±3.83	1.34	98.56±1.19
F4	4.12±0.03	3.80± 0.01	0.205	378.95±3.50	0.28	96.5 ±1.99
F5	4.18±0.5	3.80± 0.01	0.48	380.45±2.09	0.10	97.26±0.63
F6	3.95±0.2	4.10± 0.01	0.231	381.3±2.59	0.34	96.35±2.60
F7	4.15±0.6	3.70± 0.01	0.308	379.25±2.32	0.21	98.70±1.07
F8	4.06±0.5	3.75± 0.01	0.282	381.15±3.28	0.28	97.00±0.81
F9	3.87±0.2	4.10± 0.01	0.335	380.65±2.64	0.15	98.91 ±0.25

The *in-vitro* disintegration time:-

The in-vitro disintegration time is measured by the time taken to undergo complete disintegration. Rapid disintegration within several minutes was observed in all the formulations. The *in-vitro* disintegration data is tabulated in table no.26. All the formulations showed disintegration time less than 60 seconds due to wicking and swelling mechanism of superdisintegrants. The *in-vitro* disintegration time of tablets were found to be in the range of 26.83 to 43.83 sec fulfilling the official requirements.

Based on the *in-vitro* disintegration time the results of comparison of superdisintegrants SSG, croscarmellose sodium, crospovidone, in the dispersible tablets, formulation (F9) containing crospovidone (6.57%) showed least disintegration time of 26.83sec. This is because of their porous structure responsible for the faster wicking and capillary action to bringing about faster disintegration Thus; these results suggest that the disintegration times can be decreased by using wicking type disintegrant (crospovidone). It was also observed that increase in concentration of superdisintegrant, results in decrease in disintegration time. But in case of Croscarmelose, too much increase in its concentration negatively affect the disintegration.

Water absorption ratio:

Water absorption ratio, which is important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water. The formulations showed water absorption ratio in the range 69.23 to 85.61%. Formulations containing only 3.94% of superdisintegrants showed lower water absorption ratio when compared to formulations containing 6.57% of superdisintegrants. It was observed that as concentrations of CCS increases water absorption ratio increases because CCS is made by cross- linking reaction of sodium CMC. This cross linking greatly reduced water solubility of sodium CMC while permitting material to swell and absorbs water many times of its weight [15]. The values of water absorption ratio shown in Table No.5

Wetting Time:

Wetting time is another important related parameter to water absorption ratio, which needs to be assessed to give an insight into the disintegration properties of the tablets. Wetting time for all formulation batches i.e. F1 to F9 showed wide variation in the range of 34.5±0.45 to 56.93±0.05 seconds. Formulation (F9) containing MCC-200 as directly compressible filler and crospovidone used as a superdisintegrants, wetting time was found to be 34.5±0.45 seconds. Hence it was found that selected superdisintegrant and filler for study played vital role in wetting behavior, in that there was better wetting time found with crospovidone than sodium starch glycolate and croscarmellose sodium as it rapidly exhibits high capillary activity and pronounced hydration capacity.

Table No.5: In vitro Disintegrating Time, Wetting Time and Water Absorption Ratio of all formulation

F. No.	*In vitro* Disintegration time(sec)	Wetting time(sec)	Water absorption ratio (%)	Dispersion Time(Sec)
F1	43.83±2.85	56.93±0.05	69.23±2.0	79.5±1.7
F2	35.33±1.21	53.6±0.35	71.82±1.1	56.5±1.8
F3	29.33±1.75	47.96±1.3	78.31±1.0	51.7±1.7
F4	31.16±1.47	40.13±0.52	75.47±1.7	46.3±1.2
F5	35.83±0.93	49.93±0.46	83.44±1.4	53.5±1.4
F6	43.16±1.72	51.28±1.2	85.61±1.1	72.2±1.7
F7	37.5±1.37	43.26±0.3	77.54±1.4	40.2±1.2
F8	30.5±1.37	39.16±0.34	78.61±1.5	38.7±1.4
F9	26.83±2.48	34.5±0.45	80.11±1.8	31.1±1.8

Figure No.1: Comparative Profile of In Vitro Disintegration Time of All Formulations

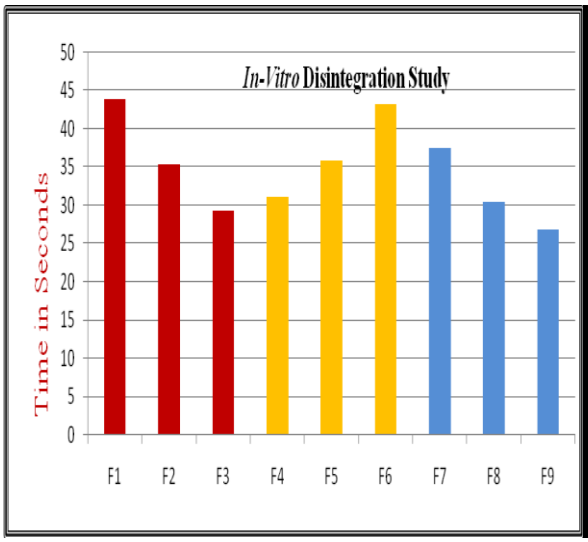
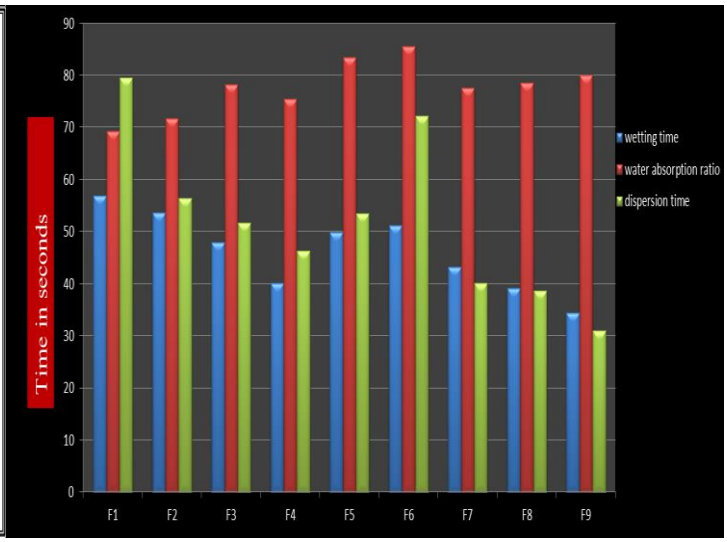


Figure No.2: Comparative Profiles of Wetting Time, Water absorption ratio and Dispersion Time of All Formulation Batches



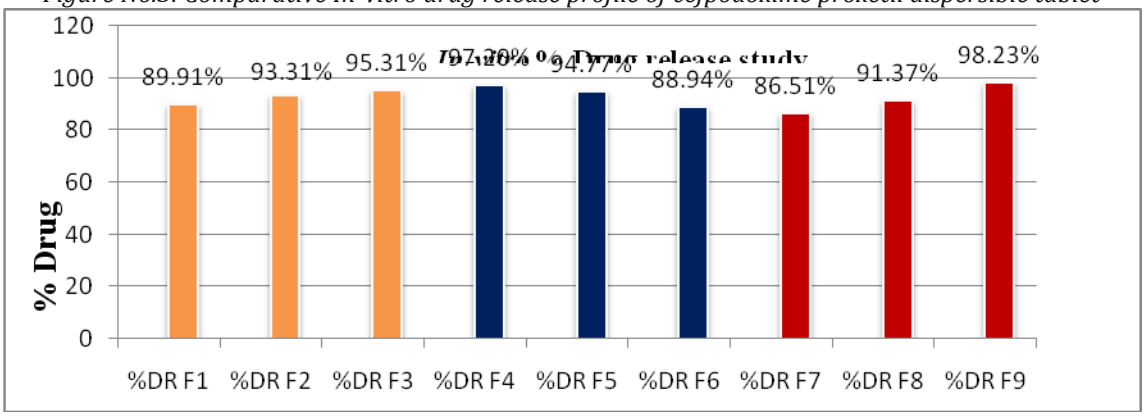
In-vitro dissolution studies:

Results of *in vitro* dissolution studies showed that Formulation Nos. F1 to F3 containing sodium starch glycolate the percent drug release values increased with increase in concentration of sodium starch glycolate. The percent drug released of F1, F2 and was found to be 89.91%, 93.31 and 95.31% respectively. Formulation Nos. F4 to F6 comprised of croscarmellose sodium used as a superdisintegrants, percent drug released are between 97.207%, 94.20 and 88.94. However, formulations F7 to F9 containing crospovidone as a superdisintegrant, percent drug released was found 86.514%, 91.37% and 98.23%. Hence, the release profile indicated that crospovidone is better than croscarmellose sodium & sodium starch glycolate as a superdintegrant to formulate dispersible tablets.

Table No. 6:In vitro dissolution: - percent drug release studies

Time (minutes)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	00	00	00	00	00	00	00	00	00
30	89.91± 1.721	93.319± 1.049	95.5± 0.56	97.207± 1.43	94.77±2 .099	88.944± 1.04	86.514± 0.68	91.374± 1.729	98.23± 0.66

Figure No.3: Comparative In-vitro drug release profile of cefpodoxime proxetil dispersible tablet



5.6. Stability studies:

The formulation F9 was selected for accelerated stability studies on the basis of their *in vitro* disintegration time, wetting time and their high % drug release. The accelerated stability study carried out at 40°C/ 75% RH for 30 days, the tablet were analyzed for drug content, *in vitro* disintegration time, wetting time, *in vitro* % drug release as shown in table No. 7.

Table No. 7: Stability study for F9

Formulation code	Time (day)	Drug content	Wetting time (sec)	*In vitro* disintegration time (Sec)	% DR in 30 (min)
F9	**0**	NA	34.5±0.45	26.83±2.48	98.23±0.66
	30	98.27±0.69	35.49±1.36	27.12±1.29	97.84±1.1

Stability study of formulation 9 was found to be stable and complies with pharmacopeial standards.

Summary and conclusion

Dispersible tablets of Cefpodoxime Proxetil were developed successfully using direct compression technique. The developed formulations were evaluated for precompression and post compression parameters as per pharmacopoeial specifications. Results of evaluation studies showed that all the formulations pass the tests for precompression parameters. The formulations containing Crospovidone showed better compressibility and flow properties compared to that of formulations contain sodium starch glycolate or Croscarmellose sodium. Direct compression as choice of method used for tablet preparations, gives the tablets with satisfactory Hardness, Friability. All the prepared formulations passes the test for Weight variation, Drug content uniformity. The results of *in vitro* disintegration test showed that increase in concentration of superdisintegrants decreased the disintegrating time up to certain limit. Above that they showed negative effect. When compared the effect of Sodium starch glycolate, Croscarmellose sodium and Crospovidone, Crospovidone showed faster disintegration. In case of test for water absorption ratio, it was increase with increase in concentration of superdisintegrants due to cross linking effect. Better wetting time was found with Crospovidone than sodium starch glycolate and Croscarmellose sodium as it rapidly exhibits high capillary activity and pronounced hydration capacity. Based on all these results obtained it was concluded that Formulation No. 9 containing 6.57% of Crospovidone showed better results compare to that of other formulations thus it was chosen as best one. Stability study on the formulation No. 9 showed acceptable stability as per ICH specifications.

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