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Formulation development & evaluation of Cefpodoxime Proxetil Dispersible Tablets

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Abstract

In present research work, dispersible tablets of cefpodoxime proxetil were formulated using direct compression technique. Cefpodoxime proxetil is an advanced-generation, broad-spectrum cephalosporin antibiotic approved for the treatment of acute bacterial exacerbation of chronic bronchitis (AECB), group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections in adult and adolescent patients. Cefpodoxime proxetil has slightly bitter taste and has poor water solubility. So in case of acute bacterial exacerbation of chronic bronchitis (AECB) group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections it require immediate release of drug from the dosage form, which make Cefpodoxime proxetil suitable candidate for dispersible tablets. In this research work, dispersible tablet for Cefpodoxime proxetil was made by Direct Compression, Croscarmellose sodium used as a superdisintegrant. It is concluded that physical parameters like hardness, thickness has significant effect on the performance of the dispersible tablet, so such parameter are critically maintained or put at their optimum level during the manufacturing of the dispersible tablets to obtain desired properties of dispersible tablets. F8 formulation shows superior result then other formulation disintegration time, cumulative percentage drug release and dispersion time were 47 seconds, 97.7% and 16 seconds respectively. Thus F8 formulation gives better disintegration time, optimum friability and drug release then other formulation.

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Key words:
Dispersible tablet, pharmaceutical excipients, disintegrant.

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INTRODUCTION

Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some

after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated [1].

Tablets are the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. But pediatric and geriatric patients may encounter inconvenience in swallowing it. To overcome this problem, in recent years increasing attention has been focused in formulating fast dissolving and dispersible tablets that are intended to dissolve or disintegrate rapidly in the mouth. Tablet disintegration has been considered as the rate limiting step in faster drug release. Developing a solid oral dosage form in today's market can be challenging. There are many pressures to discover new entities and maximize the lifecycle of products while maintaining safety, cost-effectiveness, and speed to market [2].

Tablets are almost certainly the most cost-effective and efficient form of dispensing medicines. Tablet provides a versatile, compact, robust and accurate platform for drug delivery. While the functional versatility of the tablet as a dosage form has been appreciated for decades, the design versatility of the tablet has historically been underappreciated. A variety of shapes can provide distinction without compromising manufacturing requirements [3].

Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. Tablets are the most widely utilized oral dose format. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is the fast dissolving/disintegrating tablet (FDDT) [4].

Dispersible tablets are uncoated tablets intended to be dispensed in water before administration giving a homogenous dispersion. The tablets produced must have the ability to form adequate dispersion which is uniform and stable when placed in water. The chief advantage is quicker absorption and onset of clinical effects. They are generally prepared for geriatric or pediatric patients or for those who are having difficulty in swallowing tablets. They comprise of totally water soluble excipients and components.

Dispersible tablets disintegrate either rapidly in water, to form a stabilized suspension, so, it's preferred for pediatric patients who cannot swallow a solid dosage form and the API is unstable if formulated in liquid formulation, also helpful for patients having prolonged illness who are prone to nauseatic sensations if they have to swallow a tablet. The added advantage of this formulation is faster onset of action as compared to standard compressed tablet. The properties of the water dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity after dispersion are necessary to investigate during manufacturing which decides the product performance. Dispersible tablets as defined in Ph. Eur. are uncoated or film coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. Typically a dispersible tablet is dispersed in about 5-15 ml of water and the resulting dispersion is administered to the patient.

The dispersible tablets of the present invention maintain the same advantages as conventional tablets and capsules in terms of their accuracy of dosing and ease of handling. They also possess the advantages of suspensions in terms of better bioavailability and increased compliance with children, elderly and patients who have difficulty in swallowing. These tablets have low friability and therefore are easily transportable. As opposed, to a suspension, no refrigeration is required. The dispersible tablets of the present invention are meant to form a suspension and can also be administered as conventional tablet [5].

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil was obtained as gift sample from Aurobiondo Pharma Pvt. Ltd. (Hyderabad, India). Croscarmellose sodium, SLS, colloidal silicon dioxide, CCP, starch, PG starch, PEG 6000, talcum, sodium saccharin, dry orange flavour were purchased from Vishal Pharma (Baroda, India).

Preformulation studies

Compatibilities studies

Compatibilities studies were carried out by mixing the pure API with various excipients in different proportions. Studies were carried out in flint vials at three conditions, 25°±2°C / 60%±5%RH, 40°±2°C / 75%±5%RH. The studies were conducted for 4 weeks and compared with control. Physical observations of the blend were recorded at regular interval of one week [6].

Solubility studies

Solubility studies were carried out in various solvents and it was soluble in methanol, slightly soluble in chloroform, practically insoluble in water and hot water [7].

Differential scanning calorimetry studies

DSC study was carried out using DSC-60 instrument (M/s Shimadzu) to check the compatibility of ingredients. DSC thermo gram of pure drug (Cefpodoxime proxetil), Superdisintegrant (Cross Carmellose sodium) and starch, Sodium Saccharine taken for their endothermic reaction. Finally physical mixture of all above ingredients was scanned for DSC.

Preparation of tablets using super disintegrant

Tablet formulation each containing 140 mg of Cefpodoxime proxetil were developed as per formula given in the table by compression technique using Croscarmellose sodium (Ac-Di-Sol) as binder. The excipients such as glidant, binder, flavoring agents were added and final mass was produced and compressed using rotary tablet machine. The tablet was stored in tightly closed container and evaluated for certain parameters [8].

Table 1: Formulation table cefpodoxime proxetil dispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug	140	140	140	140	140	140	140	140
Aerosil	9.0	9.0	9.0	6.0	6.0	4.0	4.0	4.0
Cross carmellose sodium.	10.0	10.0	10.0	20.0	20	15	10	10
Microcrystalline cellulose powder	100	105	130	50	40	30	15	-
Starch I.P.	35	35	35	50	30	10	-	-
Base of MCCP & Starch I.P.				118	118	143	156	167
PG Starch	100	100	80	-	50.0	40.0	30.0	25
PEG 6000	10	5	-	-	-	-	-	-
SLS	-	-	-	-	-	2.0	4.0	8.0
Talcum	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Mg.stearate	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4. 0
Sodium Saccharin	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Dry orange Flavour	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Total wt.(mg)	420.00	420.00	425.00	400.00	420.00	400.00	375.00	370.00

Table 2: Final optimized formulation

No.	Ingredients	Final formulation
1	Drug	140
2	Aerosil	4.0
3	Cross Carmellose sodium	10.0
4	Microcrystalline Cellulose powder	-
5	Starch I.P.	-
6	Base of MCCP and Starch I.P.	167
7	PG Starch	25
8	PEG 6000	-
9	SLS	8.0
10	Talcum	4.0
11	Mg.stearate	4.0
12	Sodium Saccharin	4.0
13	Dry orange flavor	4.0
	Total wt.	370.00

(Quantity in mg of excipients used in preparation of 370 mg of cefpodoxime proxetil dispersible table).

EVALUATION TESTS

Weight Variation Test

Weigh 20 tablets individually, calculate the average weight, and comparing the individual tablet weight to average weight. No more than 2 tablets are outside the percentage limit and if no more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit then the test is passed [9].

Hardness Test

Tablet requires certain amount of strength or hardness and resistance to friability to with stand mechanical shock of handling in manufacture, packaging and shipping. Tablet hardness is defined as the force requires to break a tablet in diametric compression test and hardness is thus termed as tablet crushing strength. The instruments which are use for the hardness study are known as hardness tester. The examples of hardness tester are Monsento, Pfizer, Strong-cobb, Erweka and Schleunizer. In Pfizer tester the tablet is compressed between a holding anvil and a piston connected to a direct force reading gauge. A reading is obtained with the help of indicator situated on P-Fizer hardness tester [9]

Thickness

Tablet was selected at random from individual formulations and thickness was measured by using Vernier caliper scale, which permits accurate measurement. Tablet thickness should be controlled within a ± 0.5% variation of standard value [9].

Friability Test

Friability of The tablet was determined using Friability Tester made by Electro lab. Friability for the tablets was determined for 100 revolutions. Friability of the tablets should be less than 1 % [10].

Disintegration Test

The device to test disintegration use is 6 glass tube that are 3 inches long, open at the top and held against a 10 mesh screen at the bottom end to the basket rack assembly. To test for disintegration time, one tablet is placed in each tube, and the basket rack is positioned in a one liter beaker of water, simulated gastric fluid or simulated intestinal fluid at body temperature such that the tablet remain 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of beaker. A standard motor device is use to move the basket assembly containing the tablet up and down through a distance of 5-6 cm at a frequency of 28-32 cycles per minute. To be in compliance with USP standards the tablets must disintegrate and all the particles must pass through 10 mesh sieve in the time specified [11,12].

Dissolution Test

In vitro dissolution study of tablet was conducted using USP apparatus 2, using 900 ml of 0.1 N HCl as dissolution media. Sample was withdrawn at 30 min interval, diluted & absorbance was taken at 257 nm [13, 14].

RESULTS & DISCUSSION

Preformulation studies

Compatibilities studies

Compatibilities studies were carried out by mixing the pure API with various excipients in different proportions. Studies were carried out in flint vials at three conditions, 25°±2°C / 60%±5%RH, 40°±2°C / 75%±5%RH no incompatibility was seen.

Differential scanning calorimetry studies:

DSC study was carried out using DSC-60 instrument (M/s Shimadzu) to check the compatibility of ingredients. DSC thermo gram of pure drug (Cefpodoxime-proxetil), Superdisintigrant (Cross Carmellose sodium) & starch, Sodium Saccharine taken for their endothermic reaction. Finally physical mixture of all above ingredients was scanned for DSC.

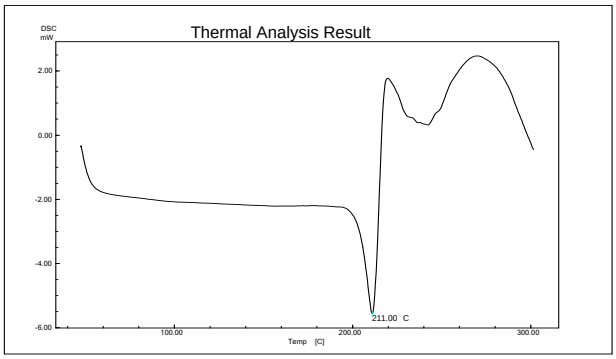

Figure 1: DSC of Reference Cefpodoxime proxetil

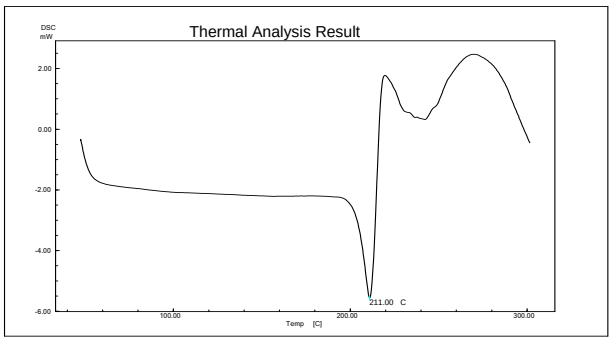

Figure 2: DSC of Sample Cefpodoxime proxetil

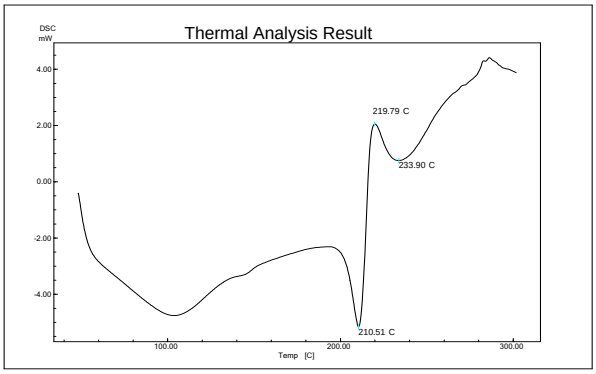

Figure 3: DSC of drug with Croscarmellose Sodium (Ac-Di-Sol) and Starch I.P.

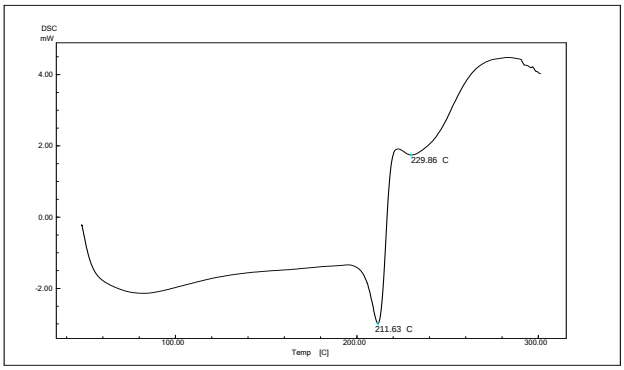

Figure 4: DSC of Drug with sodium saccharine

DSC curves obtained for pure Cefpodoxime proxetil, Superdisintegrant (Cross Carmellose Sodium) and starch, Sodium Saccharin shown in figure. Pure powdered Cefpodoxime proxetil showed a sharp melting endotherm at 210° c. DSC thermo grams of physical mixture of drug and excipients showed the melting peak of the drug at 210° c and broad endothermic peak at a sharp melting endotherm at Physical mixture of all above ingredients showed their identical peaks at defined temperature range. Presence of all peaks indicates that all ingredients are compatible with each other means there is no incompatibility between the selected ingredients.

EVALUATION TESTS OF PREPARED TABLETS

- The weight variation test of tablets was found to be as follow:

Table 3: Weight variation test of dispersible tablets.

Sr. No.	Formulation code	Avg. Weight (mg)	Result
1	F1	420 ± 0.5	Pass
2	F2	420 ± 0.7	Pass
3	F3	425 ± 0.3	Pass
4	F4	400 ± 0.8	Pass
5	F5	420 ± 0.4	Pass
6	F6	400 ± 0.5	Pass
7	F7	375 ± 0.35	Pass
8	F8	370 ± 0.23	Pass

- The hardness of the tablets was found to be as follow:

Table 4: Hardness test of dispersible tablets

Sr. No.	Formulation code	Hardness(kg/cm²) Average
1	F1	3.5
2	F2	3.5
3	F3	3.5
4	F4	3.5
5	F5	4.0
6	F6	4.0
7	F7	4.5
8	F8	5.0

- The Thickness and Friability test of the tablets was found to be as follow:

Table 5: Friability and thickness test of dispersible tablets:

Sr. No.	Formulation code	Friability (up to 1% is allowed)	Thickness (mm)
1	F1	0.82	3.7
2	F2	0.57	3.6
3	F3	0.4	3.5
4	F4	0.29	3.5
5	F5	0.28	3.5
6	F6	0.27	3.4
7	F7	0.26	3.3
8	F8	0.25	3.2

- The disintegration and dissolution time of the tablet was found to be as Follow:

Table 6: Disintegration & dissolution time of dispersible tablets

Sr. No	Formulation code	Disintegration time(sec)	Cumulative % drug release at 30 min
1	F1	80	93.4
2	F2	72	93.6
3	F3	66	94.5
4	F4	61	96.5
5	F5	59	96.7
6	F6	54	97.4
7	F7	49	97.6
8	F8	47	97.9

From the above data we can conclude that the disintegration time of the tablet formulation F8 was superior then other formulation

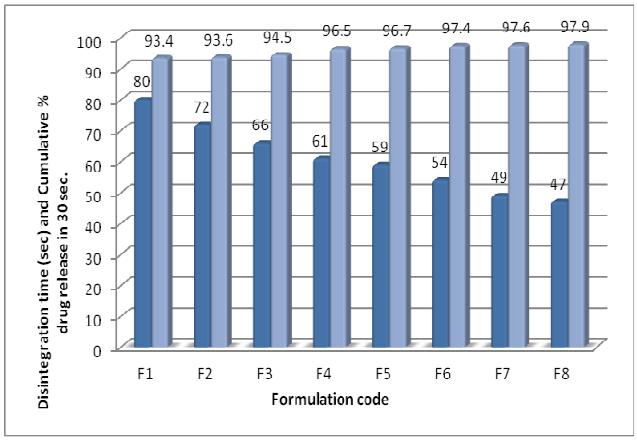

Figure 5: Graph of formulation code v/s Disintegration time (sec) and Cumulative % drug release at 30 min

- The dispersion time of the tablet was found to be as Follow:

Table 7: Dispersion Time (Second) of tablets

Sr. No.	Formulation code	Dispersion Time (When Tablet Start to Disintegrate) (Second)
1	F1	40 sec
2	F2	37 sec
3	F3	32 sec
4	F4	25 sec
5	F5	23 sec
6	F6	20 sec
7	F7	18 sec
8	F8	16 sec

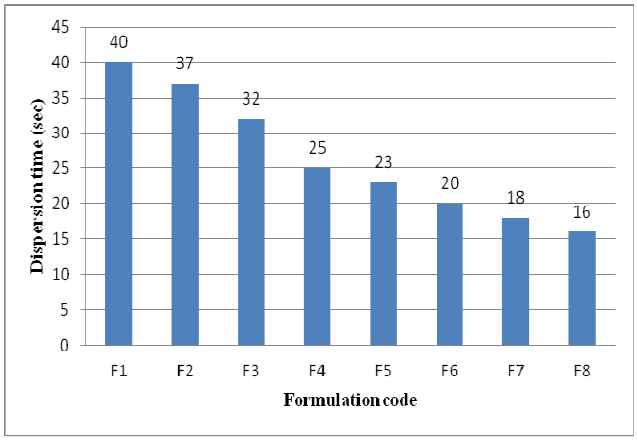

Figure 6: Graph of formulation code v/s dispersion time (sec)

CONCLUSION

In present research work, dispersible tablets of cefpodoxime proxetil were formulated using direct

compression technique. Cefpodoxime proxetil is an advanced-generation; broad-spectrum cephalosporin antibiotic approved for the treatment of acute bacterial exacerbation of chronic bronchitis (AECB), group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections in adult and adolescent patients. Cefpodoxime proxetil has slightly bitter taste and has poor water solubility. So in case of acute bacterial exacerbation of chronic bronchitis (AECB) group-A beta-hemolytic streptococcal pharyngotonsillitis, and uncomplicated skin/skin structure infections it require immediate release of drug from the dosage form, which make Cefpodoxime proxetil suitable candidate for dispersible tablets. The dispersible tablet of Cefpodoxime proxetil was made by Direct Compression, Croscarmellose sodium used as a superdisintegrant. From all above study it is concluded that process parameter like hardness, thickness & friability has great influence on performance of the dispersible tablet. Cefpodoxime Proxetil having a gel forming property so it can be used in a micronized form over a powder or compact form. Preformulation protocol was carried out by mixing the pure API with various excipients in different proportions studies shows good compatibility. Also when hardness kept low with more thickness it gives less Disintegration time and better release profile. Hence, it is concluded that Physical parameter like hardness, thickness has significant effect on the performance of the dispersible tablet, so such parameter are critically maintained or put at their optimum level during the manufacturing of the dispersible tablets to obtain desired properties of dispersible tablets. F8 formulation shows superior result then other formulation disintegration time, cumulative percentage drug release and dispersion time was 47 seconds, 97.7% and 16 seconds respectively. Thus F8 formulation gives better disintegration time, optimum friability and drug release then other formulation.

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