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PAEDIATRIC DISPERSIBLE TABLETS CONTAINING CEFDINIR (CEF) - CYCLODEXTRIN INCLUSION COMPLEX: FORMULATION AND EVALUATION

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Abstract: Cefdinir (CEF), [6R-[6α,7β(Z)]-7-[(2-amino-4-thaizolyl) (hydroxyimino) acetyl] amino]-3 –ethenyl-8-oxo-5-thia-1-azabicyclo [4.2.0]-oct-2-ene-2-carboxylic acid, is a semi synthetic third generation oral cephalosporin used in treatment of acute chronic bronchitis, rhinosinustis and pharyngitis. The absorption of orally administrated CEF is low with an oral bio-availability of 21-26%, which is mainly due to its poor aqueous solubility and slow dissolution rate. In present work paediatric dispersible tablet containing Cefdinir inclusion complex with β-Cyclodextrin (βCD) by microwave irradiation method have been developed by direct compression method, using various super disintegrants like Primogel and Ac-Di-Sol and diluents like Dicalcium phosphate (DCP), Avicel, starch 1500. The tablets were evaluated for the standard of dispersible tablets like in vitro disintegration time. The tablets formulated with Primogel and starch 1500 showed shortest disintegration time and this C3 batch is emerged as the overall best formulation batch and evaluated for thickness, weight variation, hardness, friability, drug content uniformity and in vitro release. The *in-vitro* release of batch C3 tablets were evaluated together with that of commercially available Cefdinir tablets (ADCEF TAB-125mg) in phosphate buffer (pH 6.8) for 45mins. After 45 mins ADCEF TAB released only 87.5% of drug as compared to 99% release by batch C3 tablets.

Keywords: Cefdinir; β-Cyclodextrin; Superdisintegrant; Paediatric

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INTRODUCTION

In recent years, WHO expert forum proposed a shift of paradigm towards solid oral dosage forms for paediatric medicines. Previously, formulations of choice for paediatric population were liquid formulations. To include medication for developing countries, the recommendations would have to consider the requirements for different climate zones. High temperatures often cause stability problems for liquid formulations. Further, high costs for transportation and storage have to be taken into account. Therefore, liquids should be avoided whenever possible and solid dosage forms, which fulfil desired properties for paediatric use, are highly recommended for global use[1]. Child-appropriateness of a dosage form is indicated by easy administration, swallowability, palatability and as well as the use of safe, well-established and stable excipients.

CEF, [6R-[6α,7β(Z)]-7-[(2-amino-4-thaizolyl) (hydroxyimino) acetyl] amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid, is a potent and commercially available semi synthetic third generation oral cephalosporin, displaying antibacterial properties that is used in the treatment of acute chronic bronchitis, rhino sinusitis and pharyngitis .However delivery of CEF was limited, because of its poor water solubility when given orally[2, 3]. Cyclodextrin and its derivatives have played a very important role in the formulation of poorly water soluble drugs by improving apparent drug solubility, stability and bioavailability. Furthermore, such complexes have the capability to reduce bitterness, unpleasant odour and to decrease tissue irritation upon dosing[4, 5].

In our previous studies we have proved with various characterization methods like NMR, XRD, FTIR, SEM and DSC that a stable complex has been formed between CEF and β cyclodextrin with Microwave irradiation method[6]. So in present study we aimed at developing a paediatric dispersible tablet containing CEF inclusion complex with β-CD, prepared by microwave irradiation method, to improve the solubility, swallowability, palatability and onset of action of CEF.

2. MATERIALS AND METHODS

2.1. Materials

CEF was kindly gifted by Alkem Research Lab. Ltd (India). β-CD (MW-1135), Primogel, Ac-Di-Sol were gifted by the Signet Chemical Corporation (India) and Starch 1500, DCP were received as a gift sample from Colorcon. These chemicals were used as received without further treatment. All other reagents were of analytical reagent grade purity. Double distilled water was used throughout the study.

2.2. Preparation of CEF inclusion complex

The CEF inclusion complex was prepared by using microwave irradiation method as reported previously[7, 8]. Homogenous powder mixture of CEF and β-CD was prepared in molar ratio 1:1. Minimum volume of 66% alcohol was added to homogenous mixture of CEF and β-CD, sonicated for 5 mins and subjected to microwave irradiation in a scientific microwave oven (CATA-4R). The process was carried out at power 245 watt at 60 °C for 90 seconds. After the reaction was completed, adequate amount of solvent (66% alcohol) was added to remove the residual CEF and β-CD, then the precipitate was filtered and sample was then dried under vacuum.

2.3. Preparation of tablets

Compositions of 9 different formulations of CEF tablet were prepared. Tablets composition based on weight are shown in Table 1. All ingredients were passed through sieve no.120, and then inclusion complex (87.9%) was blended with (0.02%) superdisintegrant (Primogel and Ac-Di-Sol) and 10.03% of diluents (DCP, Avicel and Starch 1500) and subsequently mixed with talc and magnesium stearate which are used as lubricants. The resulting powder mixtures were directly compressed on a single station compression machine using 13 mm standard concave punches.

2.4. Evaluation of pre-compression parameters

2.4.1. Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is determined by the funnel method. Angle of repose value less than 30° shows the free flowing property of material[9]. Angle of repose was determined by the following formula:

$$\text{Angle of Repose } (\theta) = \tan^{-1} (2h/d)$$

where, 'd' is the diameter of pile and 'h' is the height of pile.

Bulk density

Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as g/ml[9].

Bulk Density = Mass of bulk drug / Volume of bulk drug

2.4.2. Tapped density

Blend was taken and filled in 10 ml measuring cylinder which was tapped until the constant height was obtained[9].

Tapped density = Mass of bulk drug / Volume of bulk drug on tapping

2.4.3. Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow [9]. It is given by % compressibility and calculated as,

% Compressibility = (Tapped density – Bulk density / Tapped density) x 100

2.4.4. Hausner's ratio

Hausner's ratio is an index of ease of powder flow and is calculated by following formula [9]:

Hausner's Ratio = Tapped density / Bulk density

2.4.5. Bulkiness

Specific bulk volume or reciprocal of bulk density is called as bulkiness or bulk. The bulkiness was calculated by the following formula[9]:

Bulkiness = 1/Bulk Density

2.5. Evaluation of post-compression parameters of Tablets

2.5.1. Thickness and Diameter

Dimension of the tablets was measured by using a calibrated dial calliper. Five tablets of each formulation were picked out randomly and their thickness and diameter was measured individually[10, 11].

2.5.2. Hardness

Five tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester. The mean values and standard deviation for each batch were calculated[11].

2.5.3. Weight variation

The procedure described in Indian Pharmacopoeia (IP, 1996) was employed to determine the weight variation of the tablets. Ten tablets were randomly selected from each batch and weighed on an electronic balance and mean weight was taken. Each tablet was then weighed individually and standard deviation in weight was calculated for each batch[12, 13].

2.5.4. Friability

Friability indicates the ability of a tablet to withstand mechanical shocks while handling. Friability of the tablets were determined using Roche Friabilator and is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions and then the tablets were weight again (W_{final}). The loss in tablet weight due to abrasion or fracture was the measure of tablet friability [11]. Percent friability (f) was calculated by using the following formula:

$f = [(W_{initial}) – (W_{final}) /(W_{initial})] x 100$

% friability of less than 1 % is considered acceptable.

2.5.5. Wetting time

A piece of tissue paper folded twice was placed in a small petri-dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured[14].

2.5.6. Drug content uniformity

10 tablets were weighed and finely powdered. An amount equivalent to 100 mg of CEF was dissolved into sufficient quantity of methanol and sonicated for 45 mins and volume was made up to 100 ml. Resulting solution was filtered and drug content was assayed spectrophotometrically at 287 nm after proper dilutions using spectrophotometer (Shimadzu, Japan, UV 1700 Pharma Spec)[11].

2.5.7. Disintegration test

It was carried out as per the test described under disintegration time test for dispersible tablets, Indian Pharmacopoeia 2007, using water at 24 – 26 °C. The tablets should disintegrate within 3 minutes[10, 11].

2.5.8. In vitro drug release studies

The *in vitro* drug release studies of CEF from the tablets were carried out using USP dissolution test apparatus type-II (Paddle type) in 900 ml of dissolution medium (Phosphate buffer pH 6.8) at 37±0.5°C temperature and rotation speed of 50 rpm. At predetermined time interval (10, 20, 30, 45 and 60 mins). 5 ml samples were collected and immediately replaced with an equal volume of fresh medium. Samples were suitably diluted and analyzed by using UV spectrophotometer (Shimadzu 1700, Japan) at 287 nm. All the tests were carried out in triplicate and the graph of % drug release Vs Time was plotted[15].

2.5.9. Stability Study

In any rational design and evaluation of dosages forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal condition of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out accelerated stability studies, were the product is stored under extreme condition of temperature and humidity. In the present study, stability studies were carried out on selected formulation under the following condition for one month period as prescribed by ICH guidelines for accelerated study at 40 ± 2 °C and RH 75 % ± 5 %. The tablets were withdrawn after a period of 30 days and analyzed for physical characterization, dissolution and drug content [16].

3. RESULTS

3.1. Evaluation of pre-compression parameters

The flow properties of the powder mixture are important for the uniformity of mass of tablets. All 11 batches (including C4 as controlled batch with superdisintegrant and C5 as physical mixture) showed the value of angle of repose ranged from 15 to 30, indicating good flow properties. Low Hausner's ratio (≤1.16) and compressibility index (≤14.1) values indicating that all the formulations showed good compressibility. Bulkiness was found to be in the range of 2-3 as shown in Table 2.

3.2. Evaluation of tablets

The most important parameter in development of paediatric dispersible tablet is the disintegration time of tablets. Disintegration time of A1-A3 batches which contains dicalcium phosphate as the diluent were in range of 5 mins 15 sec to 4 mins 7 sec as given in Table 3.

Disintegration time of batches B1-B3 which contained Avicel PH 102 as diluent, was in the range of 4 mins 32 sec – 3 mins 53 sec whereas batches C1-C3 which contained starch 1500 as diluent showed distintegration time in range of 3 mins 10 sec – 2 mins 15 sec as shown in Figure 1. As we replaced some part of diluent with superdisintegrants like Ac-Di-Sol and Primogel, thus wetting and disintegration time decreased.

Batch C3 which contained Starch 1500 as diluent and Primogel as super disintegrant, was selected for further dissolution studies as disintegration time (2 mins 15 sec) was lower in comparison to other batches and also complying the pharmacopoeial standards of dispersible tablet must disintegrate within 3 min[12].

Table 4 showed physical parameters of selected C3 batch as it showed minimum disintegration time. The batch passed the weight variation and percentage drug content test as acceptance criteria. Hardness of the batch was 3.5±5 kg/cm^2. The friability of the batch was within acceptable limits (less than 1%) ensuring mechanical stability of formulated tablets and wetting time was found to be 15 sec.

3.3. In vitro dissolution test

In vitro release of the selected batch C3 was determined using USP II apparatus and compared with the C4 (tablet made with same formula containing plain drug) and C5 (tablet made with physical mixture) (Figure 2).From the result it is evident that, the tablet formulated with inclusion complex showed faster rate of drug release. At the end of 45 mins, the extent of drug released was 99.02%. On other hand total drug released at the end of 45 mins was 61.24 and 63.06% for the batches C4 and C5 respectively.

3.4. Comparison of inclusion complex with marketed formulation

Finally *in-vitro* drug release studies of batch C3 (inclusion complex tablet) was compared with that of marketed formulation (ADCEF DT®-TAB 125 mg) in 900 ml of dissolution medium (Phosphate buffer pH 6.8) at 37 °C temperature and rotated at 50 rpm. Higher extent of drug release (99.02%) was observed in 45mins for selected formulation C3 batch as compared to that of marketed formulation (87.50%), which indicated higher dissolution rate in selected formulation compared to marketed formulation (Figure 3).

3.5. Stability study

Stability study was carried out on selected tablet formulation. Formulation was stored at 40ºC ± 2ºC / 75 ± 5 % RH for 30 days. Dissolution profile of selected C3 batch before and after stability study was shown in Figure 4. As there is no significant changes were found during study period. Thus the formulation was found to be stable.

4. DISCUSSION

From results, it is clear that when we prepared complex of drug cefdinir with cyclodextrin by the method of microwave irradiation, the flow properties and the compressibility is as good as the pure drug. So easily we can convert this complex into tablet by adding excipients like super-disintegrant and diluents. The most important parameter for dispersible tablet is disintegration time. Out of 11 batches we prepared, batch C3 which contained primogel as super-disintegrant showed least disintegration time of 2 mins and 15 sec and this was satisfying the pharmacopoeial standards. Along with good disintegration time batch C3 tablet passed various tests like friability, weight variation and percentage drug content. We have used 6.8 phosphate

buffer as dissolution media and inclusion complex tablet (batch C3) showed 99.02% drug release after 45 mins as compared to pure drug tablet which showed only 61.24% drug release in the same dissolution media . Finally for commercial aspect and novelty we compared *in-vitro* release of this preparation with the marketed formulation in the same dissolution media. From results, it has been proven that Batch C3 tablets showed higher drug release profile as compared to marketed one. As we know stability of this preparation is also important for its commercial aspect, so after performing stability studies on this formulation, we came to know from results that formulation C3 was more stable, as there were no significant changes during study period of stability studies.

In this research we have used a special ingradient β-cyclodextrin (β-CD). This β-CD has increased the cost as well as the size of the tablet as compared to marketed tablet of cefdinir of 125mg dose. But this cyclodextrin after forming complex with cefdinir, has increased the bioavailibility of the drug by increasing its solubility [6, 17, 18]. As bioavailibility has increased automatically dosing frequency of drug will decrease and it would reduce the cost of treatment. To overcome the size issue we have converted it into dispersible tablets for paediatric patients, so that they will not face difficulty to swallow complexed tablet. Along with cyclodextrin, which helps in masking bitter taste of drug, we also added vanilla flavour to increase patability of the paediatric tablet. So this preparation could be a better substitution for the present marketed formulation of the same drug.

5. CONCLUSIONS

The CEF paediatric dispersible tablets containing inclusion complex and super-disintegrants were successfully prepared by direct compression method. Moreover, the inclusion complex provided potential advantages like reducing bitterness and to decrease tissue irritation upon dosing along with increased solubility and dissolution rate. Out of these different formulations, batch C3 has shown best dissolution profile and the lowest disintegration time in comparison to all other batches. Therefore, the batch C3 is highly promising in improving the disintegration and dissolution characteristics. As a conclusion CEF tablet (batch C3) formulated in this study can be a good alternative to the commercially available dispersible CEF tablet as it produce better dissolution profile and thereby enhancing the bioavailability of CEF.

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DECLARATION OF INTEREST

The authors report no declarations of interest.

Figure 1: Comparison of disintegration time of different batches of tablets (A1-A3, B1-B3, and C1-C3)

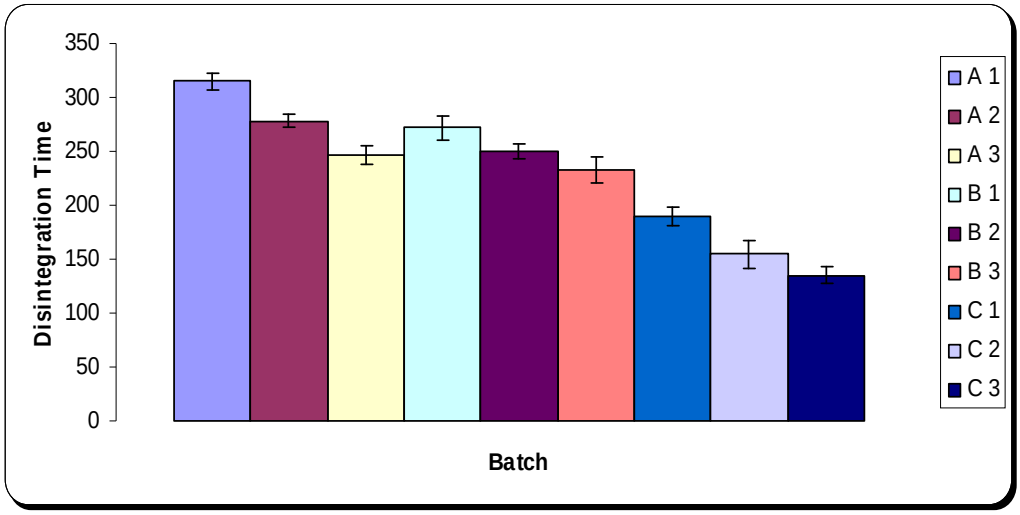

Figure 2: *In-vitro* dissolution profile of various batches of tablets like, C3, C4 and C5

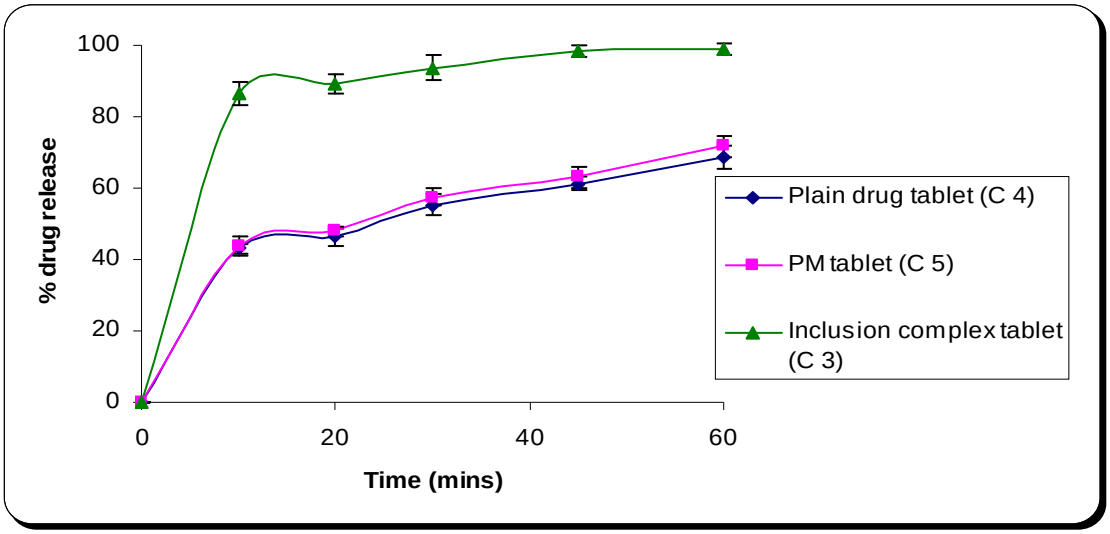

Figure 3: *In-vitro* dissolution profile of C3 batch tablets and marketed product tablets

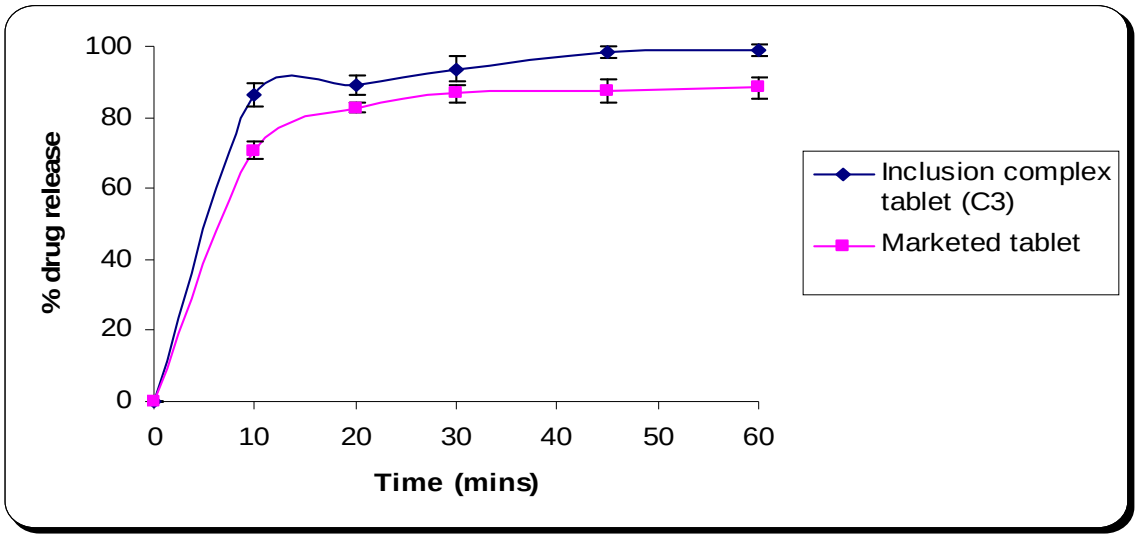

Figure 4: *In-vitro* drug release study of selected C3 batch before and after stability study

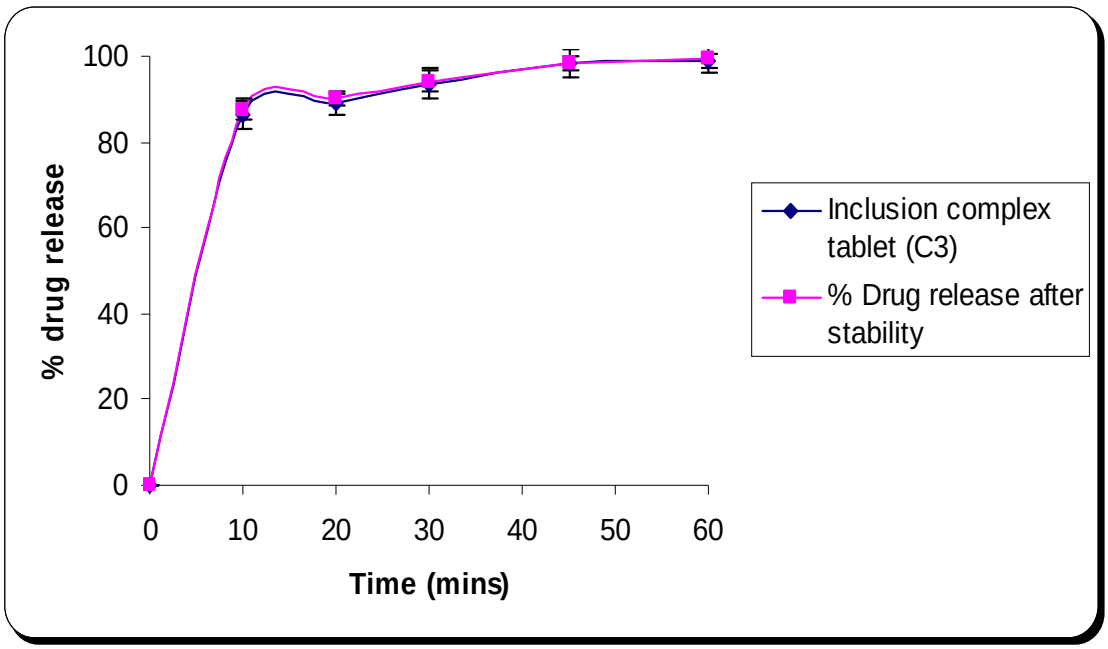

Table 1: Formulations of Cefdinir dispersible tablets

Formulation Ingredient (mg/tablet)	A1	A2	A3	B1	B2	B3	C1	C2	C3	C4	C5
Drug	-	-	-	-	-	-	-	-	-	125	-
Drug + βCD (PM)	-	-	-	-	-	-	-	-	-	-	483.8
Drug + βCD (MWI)	483.81	483.81	483.81	483.81	483.	483.	483.	483.	483.	-	-
Dicalcium phosphate	55.19	44.19	44.19	-	44.1	44.1	-	-	-	-	-
Avicel PH 102	-	-	-	55.19	-	-	-	-	-	-	-
Starch 1500	-	-	-	-	-	-	55.1	44.1	44.1	403	44.19
Ac-di-sol	-	11	-	-	11	-	-	11	-	-	-
Primogel	-	-	11	-	-	11	-	-	11	11	11
Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Mg-Stearate	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Vanilla powder	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75	2.75
Total	550	550	550	550	550	550	550	550	550	550	550

Table 2: Pre-compression parameters of all batches of tablets (A1-A3, B1-B3, C1-C3, C4 and C5)

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio	Bulkiness
A1	16.58	0.423	0.491	13.8	1.16	2.36
A2	16.25	0.425	0.482	11.8	1.13	2.35
A3	17.10	0.411	0.479	14.1	1.16	2.43
B1	15.95	0.421	0.483	12.8	1.14	2.37
B2	16.18	0.421	0.479	12.1	1.13	2.37
B3	16.10	0.422	0.481	12.2	1.13	2.36
C1	15.80	0.398	0.451	11.7	1.13	2.51
C2	15.90	0.421	0.478	11.9	1.13	2.37
C3	15.73	0.388	0.422	10.68	1.08	2.57
C4	19.14	0.411	0.485	15.2	1.18	2.43
C5	18.12	0.415	0.480	13.5	1.15	2.40

Table 3: *In-vitro* disintegration time of batches (A1-A3, B1-B3, and C1-C3)

Batch no.	Disintegration time
A 1	5 mins 15 secs
A 2	4 mins 38 secs
A 3	4 mins 7 sces
B 1	4 mins 32 secs
B 2	4 mins 10 secs
B 3	3 mins 53 secs
C 1	3 mins 10 secs
C 2	2 mins 35 secs
C 3	2 mins 15 secs

Table 4: Evaluation of post-compressional parameters of C3 formulation of Cefdinir

Code	Appearance	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug Content (%)	Wetting time (s)
C3	Off white concave tablets	4.6 ± 0.1	12.9 ± 0.1	3.5 ± 0.5	550 ± 10	0.687 ± 0.07	99.07 ± 0.52	15 ± 0.27

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