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Preparation and Evaluation of Cefixime Dispersible Tablets Using Co-Processed Excipients

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ABSTRACT

Objective: The aim of this study is to formulate a cefixime dispersible tablet and evaluate the flowability, wettability, disintegration time and *in vitro* dissolution with impact to a marketed cefixime tablet. Methods: Different formulations were prepared and tested to obtain the best formula based on disintegration time using a direct compression technique except formula (F7) which was prepared by wet granulation. Different superdisintegrants such as croscarmellose sodium (CCS) and crospovidone (CP) were used and evaluated for disintegration time. Seven formulations were prepared and evaluated for flowability, hardness, wetting time, disintegration time and *in vitro* drug release. Results: The best formulation of superdisintegrants was CP at a concentration of 10% (Formula F5) as it gave a rapid disintegration time (25 s) and less wetting time (20 s) compared to the other formulae. The formulations (F1-F6) which were prepared by direct compression method had acceptable limit of hardness (5 kg/cm^2), while F7 which was prepared by wet granulation method, had much increased hardness (10 kg/cm^2). The selected formula F5 showed an improved dissolution rate $t_{80\%}$ (0.75 minute), in comparison to Zimaks® (1.75). This may be attributed to the effect of CP that provides fast rates of dissolution of poorly soluble drugs. Conclusion: It was found that the dispersible tablets of cefixime proved to show a better release profile in all aspects as compared to the marketed formulation (Zimaks®). Using different superdisintegrants or methods of compression have significant effects on the hardness and wetting time of cefixime tablets.

INTRODUCTION

Oral drug delivery is the most favored route for the administration of various medications and tablets are the most widely accepted dosage form. Solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly patient compliance [1]. Among the major problems faced by many patients with conventional tablet dosage form is difficulty in swallowing. This problem is more apparent when drinking water is not easily available to the patient taking medicine. Dispersible tablet delivery system is characterized by fast disintegration, quick dissolving, rapid release and improved patient compliance. Dispersible tablets are either uncoated or film-coated tablets which can be dispersed within three minutes in a small amount of water or breast milk before oral administration giving a homogenous dispersion [2]. United States Food and Drug Administration (FDA) defined fast dissolving tablets as a "solid dosage forms containing medicinal substances or active ingredients which disintegrate rapidly usually within a matter of seconds when placed in water ".European pharmacopoeia also adopted the term “dispersible tablet” as a tablet that is to be placed in the water where it disperses, rapidly before swallowing [3]. Cefixime is a third generation antibiotic, which is bacteriostatic, used in the treatment of urinary tract infections, lower respiratory tract infections such as bronchitis, pharyngitis, and gonorrhea in children and elderly patients [4]. The oral dosage form absorption is between 40- 50% of cefixime from the gastrointestinal tract [5]. The oral suspension is better absorbed than tablets dosage form; therefore a dispersible tablet dissolved in water has a priority over the other dosage form.

The aim of this study is to formulate a cefixime dispersible tablet and evaluate the flowability, wettability, disintegration time and *in vitro* dissolution with impact to a marketed cefixime tablet.

MATERIALS AND METHODS

Materials

The materials used in this study are shown in Table (1).

Table (1): The materials and their suppliers used in this study

Materials	Supplier
Cefixime trihydrate	Samarra Drug Industries (SDI), Iraq
Croscarmellose Sodium (CCS),	Samarra Drug Industries (SDI), Iraq
Carboxymethyl cellulose	Samarra Drug Industries (SDI), Iraq
(CMC) and Cefixime trihydrate.	Samarra Drug Industries (SDI), Iraq
Aspartame	Furat Drug Industry, Iraq.
Crospovidone (CP)	3B Pharmaceutical(Wuhan) International Co. Ltd. China
Mannitol	Himedia Laboratories PVT. Ltd. Mumbai, India.
Mg stearate	Riedel-De-Haen AG seelze, Germany
Talc and Sodium dihydrogen phosphate.	BDH chemicals Ltd poole, England

Instruments

Table 2 shows the instruments used in this study.

Table (2): The instruments and their manufacturers used in this study

Instruments	Manufacturer
Electronic balance	Denver Instrument, Germany
Tablet machine	TDP, China
Ovens	Gallenhamp (Compenstat) oven BS, England and Memmert Oven, W. Germany
Melting point apparatus	Stuart, Copley Scientific, U.K.
Hardness tester	Stokes, Monsanto Co. Ltd., USA

pH-meter	Hanna Instrument, Italy
Sonicator	Copley Scientific 2200E, U.K.
Dissolution apparatus	Minhua Pharmaceutical Machinery co. ltd. RC-6D. China
Disintegration apparatus	Minhua Pharmaceutical Machinery co. ltd. BJ-3. China
Roche friability tester	Moor and Wright, Sheffield
Spectrophotometer	Sco tech, spuv-26, Germany

Methods

Melting point determination

Using the capillary tube method by the temperature was increased gradually. The temperature at which the powder was converted to liquid was recorded as the melting point [6].

Determination of cefixime λ_{max}

Fifty milligrams of cefixime trihydrate was dissolved in 100 ml phosphate buffer pH (7.2) to prepare 0.5 mg/mL stock solution. From this stock solution, a dilute (0.03 mg/ml) solution was prepared and scanned by a UV spectrophotometer at the range of 200-400 nm, in order to determine the wavelength of maximum absorbance (λ_{max}) of cefixime.

Several diluted samples of cefixime trihydrate were analysed spectrophotometrically at the determined λ_{max}. The absorbance obtained were recorded and plotted against concentrations to obtain a calibration curve.

Formulation of cefixime dispersible tablet

Different formulas were prepared and tested to obtain the best formula based on disintegration time as shown in Table 3. All formulas were prepared using direct compression technique except formula (F7) which was prepared by wet granulation using the formula as given in the Table 3. The drug and excipients were passed through a #60 size mesh prior to the preparation of the dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 minutes to ensure uniform mixing in geometrical ratio. Each formula was prepared by mixing all

the ingredients (except the lubricant) for 15 minutes after which the lubricant was added and blended for another minute. The final mixture of each formula was compressed using a 10 mm single punch tablet machine.

The wet granulation method was carried out for (F7) using binding agents PVP2% in isopropyl alcohol. The granulation powder was dried at 60ºC for 1 hour and passed through a sieve 20#. The lubricant was mixed 5 minutes before compression [7]. Formula (F7) was selected for wet granulation to make a comparison of the characteristic properties with the direct compression method.

Evaluation of the prepared dispersible tablets

Angle of repose

Funnel method was used; the powders were allowed to pass through a funnel and poured onto a horizontal plane, fixed base diameter (**D**). The tan of angle of repose (**θ**) was calculated after measuring the height (**H**) of the cone of the powder utilizing Equation (1).

$$Tan(\theta) = \frac{H}{0.5 \times D} \quad \text{..... Eq (1)}$$

Compressibility (Carr's index)

A sample of each formula powder, was poured into a volumetric cylinder to occupy an initial volume ($V_\circ$) and then the cylinder was subjected to a standard tapping procedure on to a solid surface until a constant volume was achieved (V_f). The compressibility index was calculated using Equation 2:

$$\text{Compressibility Index} = \frac{V_\circ - Vf}{V_\circ} \times 100 \quad \text{..... Eq (2)}$$

Wetting time

A filter paper folded twice was placed in a small petri-dish (Internal diameter = 6 cm) containing 6 ml of water at 25ºC.

A tablet was placed on the filter paper and the time required for the complete wetting of the tablet was recorded as a wetting time. The mean of three determinations was used ± SD [8,9].

Hardness

Three tablets selected randomly from each formulation batch were tested and the average reading ± SD was recorded, using Monsanto hardness tester in which the hardness was expressed as a force in kg/cm^2 required to crush the tablet.

Table 3: Composition of the prepared dispersible formulas

Component mg	F1	F2	F3	F4	F5	F6	F7*
Cefixime trihydrate	112	112	112	112	112	112	112
CCS	10 (2.5%)	20 (5%)	40 (10%)				
CP				20 (5%)	40 (10%)	60 (15%)	40 (10%)
CMC	40	40	40	40	40	40	40
Mannitol	218	208	188	208	188	168	178
PVP							10 (2.5%)
Aspartame	8	8	8	8	8	8	8
Talc	8	8	8	8	8	8	8
Mg stearate	4	4	4	4	4	4	4
Total weight(mg)	400	400	400	400	400	400	400

*Prepared by wet granulation,

112 mg of cefixime trihydrate = 100 mg of cefixime

Weight variation

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weight to the average. The deviation from the average weight of the tablet should not exceed ± 7.5% and no tablet deviates by more than 15% [10].

In vitro disintegration test

The disintegration tests were done for all cefixime containing formulas as well as conventional cefixime tablet (Zemaks) as a reference tablet by using the USP disintegration apparatus, the basket rack assembly containing six open ended tubes and 10- mesh screen on the bottom was used. The time in seconds required for complete passing of all fragment of the tablet is recorded as disintegration time of the tablet [11].

In vitro dissolution studies

In vitro dissolution studies were performed for formula (F5) and also for conventional (Zemaks) tablet as a reference tablet by using type II (paddle) dissolution apparatus at 100 rpm, and 900 ml of phosphate buffer pH (7.2) as a dissolution medium at 37°C ± 0.5°C (12). An aliquot of 5 ml of the dissolution medium was withdrawn at specific time intervals and replaced with 5 ml of the buffer and the absorbance of filtered solutions was determined using UV-spectrophotometer and drug content was determined from a standard calibration curve.

RESULTS AND DISCUSSIONS

Determination of cefixime melting point

The cefixime trihydrate was melted with decomposition over the range 218-225ºC. This result is the same as that reported [6] which indicates the purity of the drug powder.

Effect of superdisintegrants types and their concentrations on the flowability of the prepared dispersible powders

Formulas of (F1-F6) as illustrated in Table 4 showed the effect of different superdisintegrant types (CCS and CP) with different concentrations on the flowability of the prepared powders and the physical properties of the prepared dispersible tablets. In general, the results showed that all prepared powders had acceptable flow characters according to the Angle of repose value and Carr's index as shown in Table 4. These results agree with guideline of tablet flow character in British Pharmacopeia [12].

Angle of repose for all formulations were found to be between the excellent and poor value which indicate that all formulations within the acceptable limit and Carr's index was found to be less than 25% indicating good flowability.

The average weight variation, hardness and drug content for all formulations were illustrated in Table 5. These results demonstrated that all formulations were within the acceptable limit for tablets according to the British Pharmacopeia.

Table (4): Angle of repose, Carr's index and flow properties of the prepared powders

Formula no.	Angle of repose (˚)± SD	Carr's index	Flow character
F_1	32± 0.5	21.05	Good and passable
F_2	24.7 ± 0.3	19.2	Excellent and fair
F_3	29.2± 0.5	18.18	Excellent and fair
F_4	30.1± 0.5	25	Good and Passable
F_5	41± 0.6	20	Passable and Fair
F_6	48.5± 0.6	18.18	Poor and Fair
F_7	23± 0.4	15.78	Excellent and Good

Table 5: Drug content, hardness and weight variation (%) of formulations (F1-F7)

Formulation no.	Drug content ± SD *	Hardness (kg/cm^2)	Weight variation % deviation
F1	105.26% ± 0.41	5± 0.2	1.09
F2	103.63% ± 0.39	5 ±0.2	0.85
F3	100.71% ± 1.63	5 ± 0.1	0.89
F4	97.52± 0.52	5 ± 0.4	1.1
F5	97.81 ± 0.28	5 ± 0.2	0.75
F6	99.64 ± 0.71	5 ± 0.1	0.95
F7	101.12 ± 0.55	10 ± 0.1	0.9

Effect of different superdisintegrants on the disintegration and wetting times of cefixime dispersible tablets

Figure 1 show the wetting and disintegration behaviour of the dispersible tablets in water. It was observed that the wetting and disintegration time for all formulas were influenced by the concentration and type of superdisintegrant. The lowest concentration of CCS in F1 (2.5%) showed the lowest wetting and disintegration time than F2 and F3. Whereas in the presence of CP as superdisintegrant, F5 with concentration of (10%) was the lowest wetting time (25±1) seconds and disintegration time was (20±1) seconds comparing to F4 and F6 which have a wetting time of (31±1) and (65±3) respectively and disintegration time of (27±1) and (27±2) respectively. Among all prepared formula in this study, F5 was the best formula according to the wetting and disintegration time. Kalavathy and his colleagues found that crospovidone alone in a concentration of 12% for formulations of cefixime dispersible tablet gave a disintegration time of 15 seconds [13].

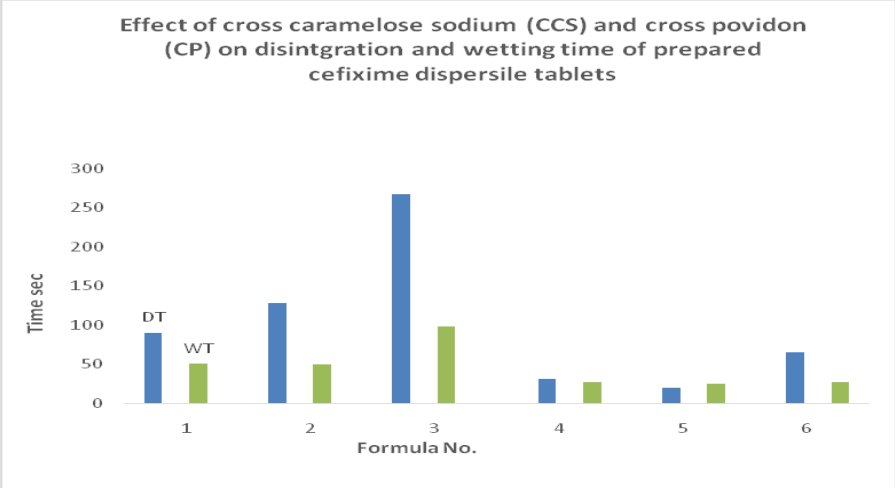

Figure 1: Wetting and disintegration times of all formulae

These results indicated that superdisintegrants play a major role in the dissolution and disintegration of the tablets. An optimum concentration of superdisintegrants should be chosen to ensure rapid disintegration and wetting time of tablets [14]. Superdisintegrants provide rapid disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution

[15]. As shown in figure (1), CCS gave a low *in-vitro* disintegration time initially and then increased at 10% (w/w). It is thought to be due to its fibrous nature of CCS which allows wicking of water into tablet matrices. Later on, swelling causes a smoothening of the particle edges as a result of which the border length per unit area decreases. Thus, at lower concentrations, the fibrous nature is more noticeable and smoothens gradually with time. While at high concentrations, there is a probability that wicking and swelling occurs simultaneously leading to smoothening the particles and the width of the pore decreases, so the disintegration time increases [16].

Effect of wet granulation method on the physical properties of the prepared dispersible tablets

The formulas 1-6 were prepared by direct compression, had acceptable hardness (5 kg/cm^2), while F7 which was prepared by wet granulation method, had much increased hardness (10 kg/cm^2).

This increased hardness led to as increased disintegration time (230 s) and also delayed the wetting time to (227 s) due to the difficulty of the penetration of water to this highly compact tablet as shown in Figure 2 which demonstrates the effect of wet granulation method in F7 with the best dispersible tablet in F5. This result proved the importance of preparation of dispersible systems among the methods of tablet preparation.

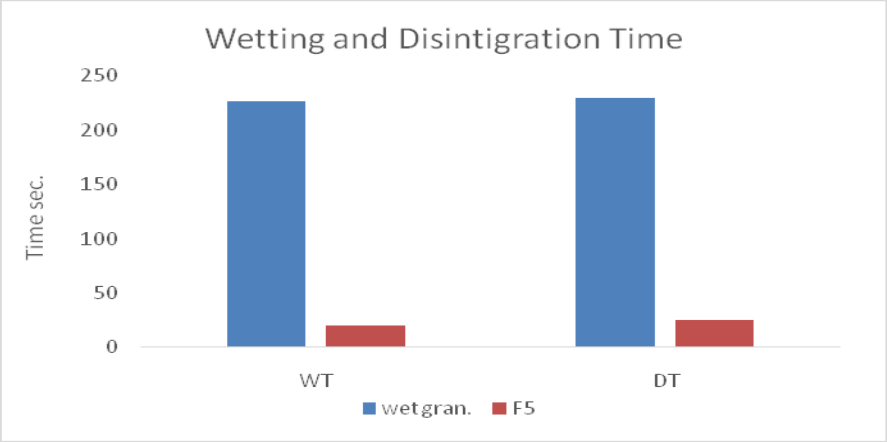

Figure (2): Effect of the preparation method on the physical properties of the prepared dispersible tablets

Comparison of selected formula 5 with cefixime conventional tablet (Zimaks®)

The selected formula (F5) showed improvement in disintegration time (25 s) compared with (103 s) for Zimaks®. This is attributed to the effect of CP that when added to tablets provide rapid disintegration since it acts by a wicking mechanism [15] as shown in Figure (3).

The selected formula F5 showed improvement in dissolution rate $t_{80\%}$ (0.75 minute), in comparison to Zimaks® (1.75), this may be attributed to the effect of CP that provides the fastest rate of dissolution of poorly soluble drugs and this will improve the drug release profile as shown in Figure (4).

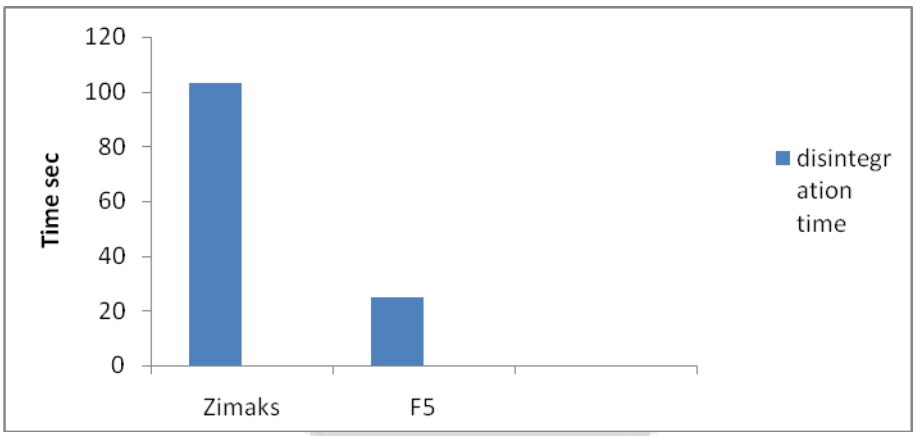

Figure (3): *In-vitro* disintegration time for the prepared dispersible tablets (F5) and conventional tablet Zimaks®

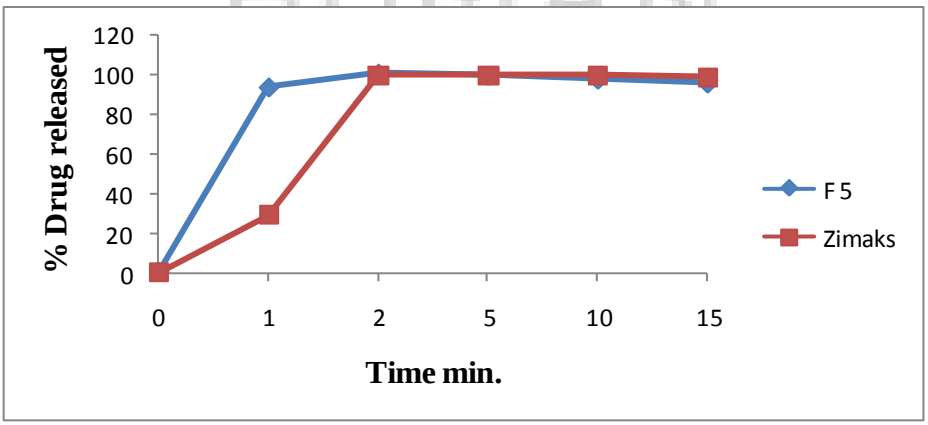

Figure (4): The dissolution profile of the prepared dispersible tablets (F5) and the plain cefixime tablet (Zimaks®) in phosphate buffer at 37°C ± 0.5 °C and 100 rpm

CONCLUSION

Water dispersible tablets were successfully formulated with acceptable flow characteristics. The type of superdisintegrant had a marked effect on the wettability and disintegration time of dispersible tablets. A conclusion can be drawn from these results that below an optimum concentration of superdisintegrant there was decreased wetting and disintegration time whereas above this concentration the disintegration time remains almost constant or even increases. Among all formulas, the best was F5. As comparison to the wet granulation method, the direct compression method of the selected dispersible tablet formula showed faster wettability and disintegration effects. The dissolution rate of the selected formula was faster than the cefixime marketed product.

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