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Preparation and In Vitro Evaluation of Orodispersible Tablets of Albendazole

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Keywords: Orodispersible tablet, banana powder, albendazole.

Abstract:

Orodispersible tablet (ODT) is a solid dosage form containing a drug substance that disintegrates and/or dissolves rapidly in the mouth without water within a few seconds to few minutes. In current study, Albendazole was selected to be formulated as a ODT. Six formulas of albendazole with three different superdisintegrating agents were prepared. Banana powder, Na croscarmellose and Na crospovidone were the chosen superdisintegrating agents. Direct compression method was employed for its simplicity and cost effectiveness. The effectiveness of the prepared formulas was tested by *in vitro* evaluation study depending on their disintegration times and drug release. Unlike croscarmellose containing formulas (F1 and F2), banana containing formulas (F3, F4 and F5) exhibited an increase in their disintegration times when their amount was increased. Although F6, that had crospovidone as a superdisintegrating agent, demonstrated an acceptable disintegration and % drug release profiles, F3 was the best formula regarding the % drug release. Hence, poor disintegration profiles do not necessitate low dissolution values of a given formulation. The delayed disintegration times of banana containing formulas could be attributed to its tendency to work as a binder. The binding tendency could be enhanced by increasing the amount of banana powder in formulations that have poor water soluble drug like albendazole.

التحضير والتقييم المختبري لقرص دواء الالبندازول المتحلل فمويا

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الكلمات المفتاحية: الاقراص المتحللة فمويا, مسحوق الموز, الالبندازول.

الخلاصة:

قرص الدواء المتحلل فمويا هو جرعة دوائية صلبة يحتوي على الدواء وله القدرة على ان يتفكك او يذوب بسرعة في الفم في غضون بضع ثوان الى بضع دقائق دون الحاجة الى استخدام الماء. في الدراسة الحالية, تم اختيار دواء الالبندازول ليتم تحضيره كقرص دوائي متحلل فمويا. تم تحضير ستة صيغ (ص) من الالبندازول باستخدام ثلاثة عوامل تفكك دوائية. مسحوق الموز, كروزكارملوز الصوديوم والكروزبوفيدون صوديوم تم اعتمادها كعوامل للتفكك الدوائي. وقد تم اعتماد طريقة الكبس المباشر في تحضير الاقراص لكونها طريقة بسيطة واقتصادية. إن فعالية الصيغ المحضرة قد تم دراستها من خلال التقييم المختبري بالاعتماد على سرعة تفكك الصيغ وسرعة تحرر الدواء من الصيغ. خلافا لصيغ الكروزكارملوز(ص1 و ص2), أظهرت الصيغ التي تحتوي على مسحوق الموز (ص3, ص4 و ص5) زيادة في اوقات تفككها مع زيادة كمية عامل التفكك الدوائي. وعلى الرغم من ان ص6 التي تحتوي على الكروزبوفيدون كعامل مفكك قد اظهرت تفكك مقبول ونسبة تحرير جيدة للدواء بالمقارنة مع باقي الصيغ, كانت ص3 افضل صيغة من بين الصيغ المحضرة جميعا في خاصية تحريرها للدواء. وبالتالي فان خاصية التفكك الضعيفة قد لاتؤدي الى قيم ذوبانية ضعيفة للصيغة نفسها. يمكن ان يعزى تأخر تفكك الصيغ المحتوية على مسحوق الموز الى ميله الى العمل كمادة رابطة حيث يمكن ان تزداد هذه الخاصية عند استخدام مسحوق الموز مع ادوية ذات ذوبانية ضعيفة كالالبندازول.

1. INTRODUCTION

The oral route for drug administration represents the most preferable way of drug administration owing to its convenience, elegancy, portability, ease of administration, dose accuracy and patient compliance. The majority of oral formulations are being formulated as tablets (1,2). Orodispersible tablet (ODT) is a solid dosage form containing a drug substance that disintegrates and/or dissolves rapidly in the mouth (either on or beneath the tongue or in the buccal cavity) without water within a few seconds to few minutes (3). Upon placement in the mouth, orodispersible tablets absorb saliva fluid rapidly into the tablet core allowing the super disintegrant to swell, rupture the tablet and liberate the components that form solution or suspension, which in turn can be swallowed easily without water. However, orodispersible tablet can also be swallowed as a conventional tablet by using water to push it down to stomach (4).

Unlike other dosage forms, the excipients for orodispersible tablets should be selected carefully. Excipients use in ODTs contain at least one superdisintegrant, a diluent, a lubricant and optionally a swelling agent, a permeability aiding agent, sweeteners and flavorings (5,6,7). ODTs are preferred for patients who cannot swallow conventional dosage forms, they could enhance the bioavailability of some drugs that undergo first pass metabolism and they provide rapid drug action for urgent medical interventions. Additionally, they allow accurate dosing compared to liquids and provide commercial opportunities such as marketing advantages and product diversity (8). Albendazole (ABZ) which is practically insoluble in water was selected to be formulated as ODT (9).

The aim of this study is to formulate an orally disintegrating tablet of albendazole with the employment of different superdisintegrating agents.

2. EXPERIMENTAL WORK

2.1. Materials

Albendazole powder (Iraq), Croscarmellose sodium (CCS), Crospovidone (CP), Sodium Saccharin, Mannitol, Methanol (India), Banana powder (China), Magnesium stearate (Mg St) and Hydrochloric acid (HCl) (Germany).

2.2. Equipment

Electrical melting point apparatus (SMP10 SIGMA, Germany), Sartorious balance (Denver Instrument, Germany), UV-Visible Spectrophotometer (SPUV-26, Germany), Ultrasonic cleaning machine (Italy), pH-meter (Hanna Instrument, Italy), Disintegration apparatus (Minhua Pharmaceutical Machinery Co. ltd. BJ-3. China), Dissolution apparatus (Minhua Pharmaceutical Machinery co. ltd. RC-6D. China), Microfilters (China), Single punch tablet machine (TDP, China), Glass Petri dishes (Wings, U.K.), Magnetic stirrer (Copley scientific, U.K.), Erweka Hardness tester (Stokes, Co. Ltd., USA).

2.3. Characterization of Albendazole

2.3.1. Determination of Albendazole Melting Point:

The melting point of ABZ was measured according to USP by capillary tube method. The tube was closed from one end while the other end was dipped in ABZ powder and placed inside the electrical melting point apparatus. The temperature began to increase gradually until the powder started to convert to liquid. This temperature was recorded as the melting point of ABZ (10).

2.3.2. Determination of λmax of Albendazole:

A solution of 20 µg/mL ABZ in 0.1N (methanolic 5%) HCI (pH= 1.2) was prepared and scanned by a UV-Visible spectrophotometer from (200-400) nm in quartz cells and the λmax was documented to be used in calibration curve determination (11). Figure 1 shows the value of the measured λmax.

2.3.3. Determination of Calibration Curve of Albendazole:

Calibration curve of ABZ was constructed by preparing serial dilutions of the drug (2.5, 5, 10, 15, 20 and 25 µg\mL) from a stock solution of 20 mg of ABZ in 100 mL of 0.1N (methanolic 5%) HCl (pH= 1.2). Samples were spectrophotometrically analyzed at the determined λmax of ABZ. The measured absorbances were recorded and plotted against the respective concentrations (11). Calibration curve of ABZ in (methanolic 5%) HCl is shown in Figure 2.

2.4. Formulation of Albendazole Orodispersible Tablets

Six formulas of albendazole orodispersible tablets were prepared with different superdisintegrant quantities. All formulas were prepared using direct compression technique. Each formula was formulated by mixing all the ingredients (except the lubricant) for 15 min after which the lubricant was added and blended for another three min. The final mixture was compressed using a single punch machine. Since ABZ is light sensitive, samples were kept in light resistant containers. ABZ orodispersible formulas were documented in Table 1.

Table 1: Composition of albendazole orodispersible formulas

Material (mg)	Formulas					
	F1	F2	F3	F4	F5	F6
ABZ	200	200	200	200	200	200
CCS	10 (2.5%)	20 (5%)	-	-	-	-
Banana powder	-	-	5 (1.25%)	10 (2.5%)	20 (5%)	-
CP	-	-	-	-	-	40 (10%)
Na Saccharin	8 (2%)	8 (2%)	8 (2%)	8 (2%)	8 (2%)	8 (2%)
Mg St	4 (1%)	4 (1%)	4 (1%)	4 (1%)	4 (1%)	4 (1%)
Mannitol	178	168	183	178	168	148
Total weight (mg)	400	400	400	400	400	400

2.5. Evaluation of the Prepared Albendazole Orodispersible Tablets

2.5.1. Weight Variation:

Weight variation was determined for the prepared ABZ orodispersible tablet according to the British Pharmacopoeia (BP) (12). Twenty tablets from each formulation were weighed individually and their average weight was calculated and documented in Table 2.

2.5.2. Hardness:

Three orodispersible tablets were selected randomly from each formulation and their hardness (kg) was tested using Erweka hardness tester (13). Results are expressed as a mean ± S.D as shown in Table 2.

2.5.3. Wetting Time:

A conventional method was used to measure the wetting time of all the prepared orodispersible formulations of ABZ. Each tablet was placed in a petri dish (5.5 cm in diameter) containing six mL of distilled water at room temperature and the time (in sec) for complete wetting was recorded (14) and demonstrated in Figure 3. The measurements were repeated three times and the mean value was calculated ± S.D as documented in Table 2.

2.5.4 *In vitro* Disintegration Test:

The disintegration test was performed using the USP disintegration apparatus. The apparatus consisting of a basket rack of six opened-end tubes with 10-mesh stainless steel wire screen. The basket was raised and lowered by 28-32 times per minute in a medium of 900 mL 0.1 N HCl where temperature was maintained at 37 ± 2 ºC. A tablet was placed in each tube of the apparatus and the time (in sec) for complete disintegration was recorded (15). Results are reported in Table 2.

2.5.5 *In vitro* Dissolution test:

Dissolution test was performed for tablets of the prepared formulas using Type II (paddle) dissolution apparatus. A tablet was placed in the 1000-mL glass vessel of the apparatus which was prefilled with 900 mL of 0.1 N HCl (pH= 1.2) as a dissolution medium. The apparatus was adjusted at constant stirring speed of 50 rpm and the temperature was maintained at 37°C ± 0.5 °C. A five mL sample of the medium was withdrawn and replaced by the same volume of fresh dissolution medium at specified time intervals for 30 minutes. Samples were filtered through microfilter and analyzed spectrophotometrically at the λmax of albendazole (12). Dissolution profiles of the prepared formulations are reported in Table 3 and demonstrated in Figure 5.

2.5.6 Statistical Analysis:

A statistical analysis was computed to observe the correlation between the wetting and disintegration times of the prepared formulas. The results were summarized in scatterplot as shown in Figure 4. Analysis was determined at 95% confidence interval using GraphPad Prism 6 Demo program.

3. RESULTS

3.1. Characterization of Albendazole

3.1.1. Determination of Albendazole Melting Point

The melting point of albendazole powder was 208 ºC which is within the reported range of (208-210) ºC (10).

3.1.2. Determination of λmax of Albendazole

The UV scan of albendazole in 0.1N (methanolic 5%) HCI (pH 1.2) showed a peak at 295 nm which was regarded as the λmax as shown in Figure 1. This result is similar to the documented scan (11).The documented λmax was referred in the quantitative study of ABZ.

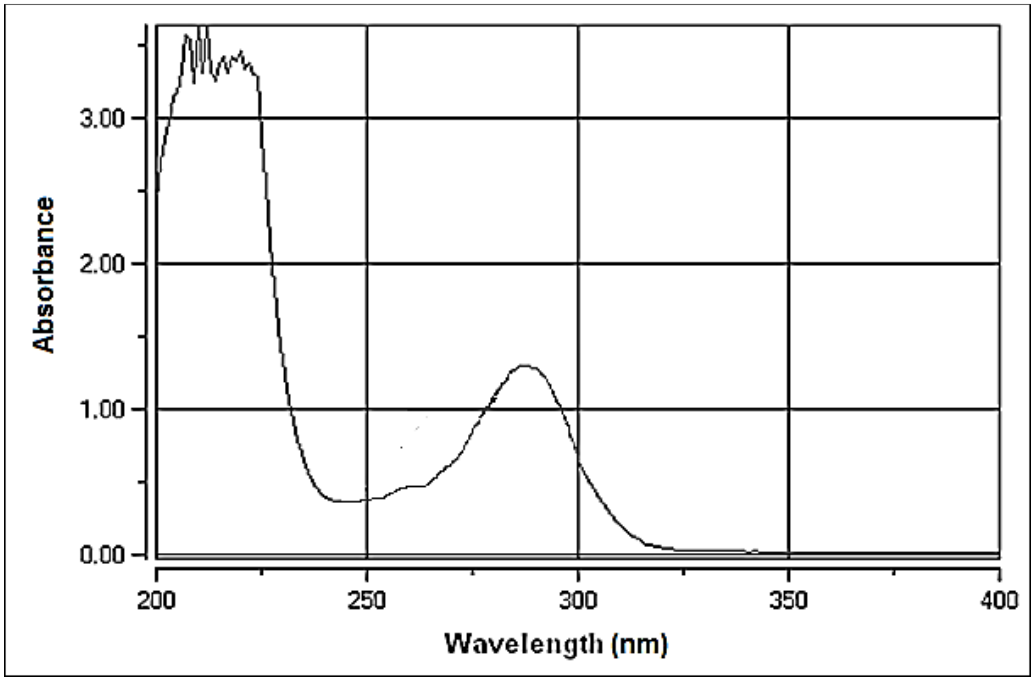

Figure 1: UV scan of albendazole within the range (200-400) nm in 0.1N (methanolic 5%) HCI (pH = 1.2) showing λmax at 295 nm

3.1.3. Determination of Calibration Curve of Albendazole

The calibration curve of ABZ in 0.1N (methanolic 5%) HCl is shown in Figure 2. A straight line with high regression coefficient (R^2 = 0.9972) was obtained by plotting the absorbance (nm) versus the concentration (µg\mL).

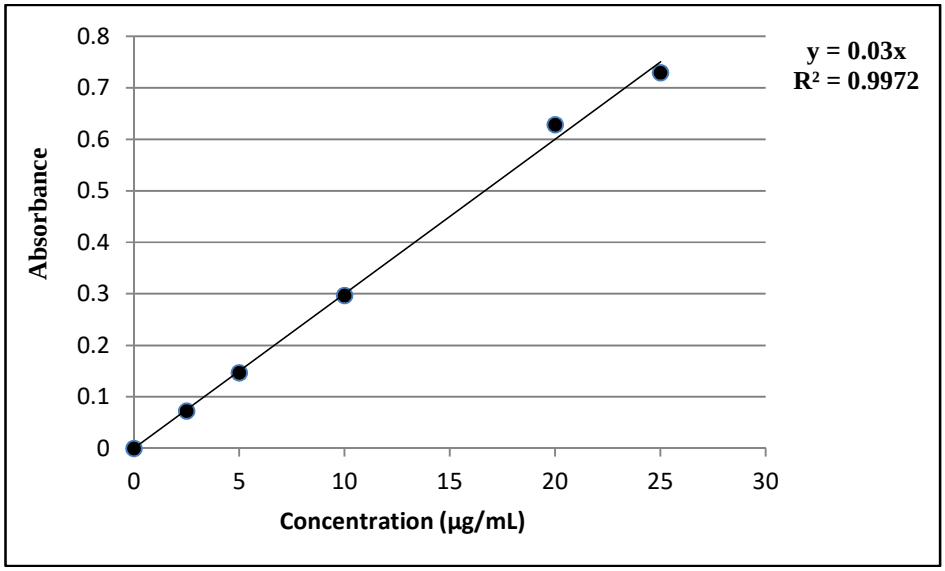

Figure 2: Calibration curve of albendazole in 0.1N methanolic HCl (pH 1.2) at λmax of 295 nm

3.2. Evaluation of the Prepared Albendazole Orodispersible Tablets

3.2.1. Weight Variation

Table 2 shows the average weight of the tablets. The measured weights complied with BP criteria (12).

3.2.2. Hardness

The hardness of the prepared orodispersible tablets was kept near 3.5 (kg) as shown in Table 2. The achieved hardness was in accordance with literature values for the hardness of orodispersible tablets (13).

3.2.3. Wetting Time

Wetting times in seconds (mean ± SD) of the prepared orodispersible formulations of ABZ are documented in Table 2. Figure 3 shows a completely wetted tablet (14).

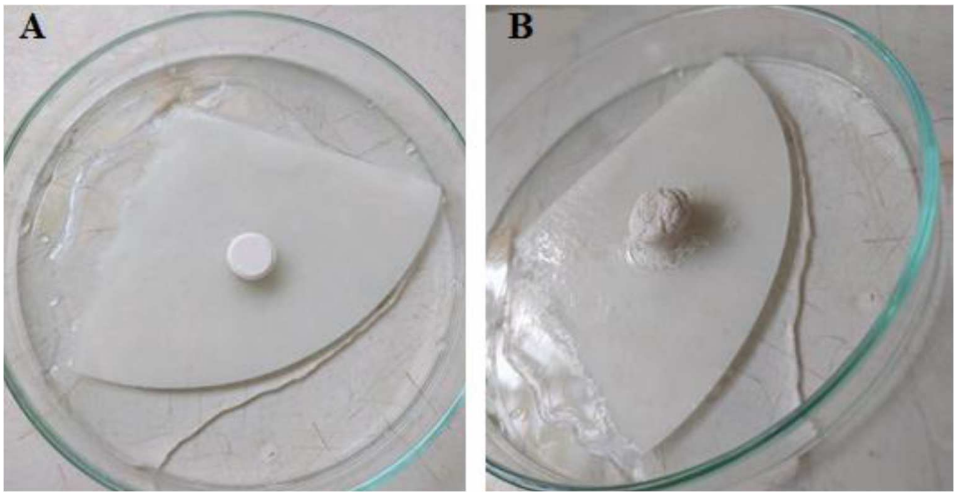

Figure 3: Wetting test of ABZ ODT

(A) Resembles an ODT of ABZ of F2. A tablet was placed in a Petri dish which contained a folded filter paper and filled with 6 mL distilled water.

(B) Resembles a completely wetted ODT of ABZ of F2. Complete wetting was achieved after 31 seconds.

3.2.4. *In vitro* Disintegration Test

Table 2 shows the reported disintegration times (sec) of the orodispersible tablets (15).

Table 2: The results for weight variation, hardness, wetting time and disintegration time of ABZ ODT formulations

Formula	Weight Variation (mg)*	Hardness (kg)**	Wetting Time (sec)**	Disintegration Time (sec)***
F1	392 ± 3.6	3.5 ± 0.5	45 ± 0.3	30 ± 7.8
F2	396 ± 2.5	3.5 ± 0.3	30 ± 1.5	20 ± 8.0
F3	396 ± 0.6	3.5 ± 0.1	60 ± 1.2	160 ± 15.1
F4	394 ± 4.1	5.0 ± 0.2	180 ± 0.6	220 ± 8.4
F5	395 ± 3.4	3.5 ± 0.2	185 ± 9.4	280 ± 5.5
F6	396 ± 2.8	3.5 ± 0.2	32 ± 0.2	22 ± 5.0

All values were expressed as mean ± SD

*** (n=20), ** (n=3), *** (n=6).**

3.2.5. Correlation between wetting and disintegration times

There was a strong positive correlation between the two variables, (r = 0.9258, p = 0.0081) as demonstrated in Figure 4.

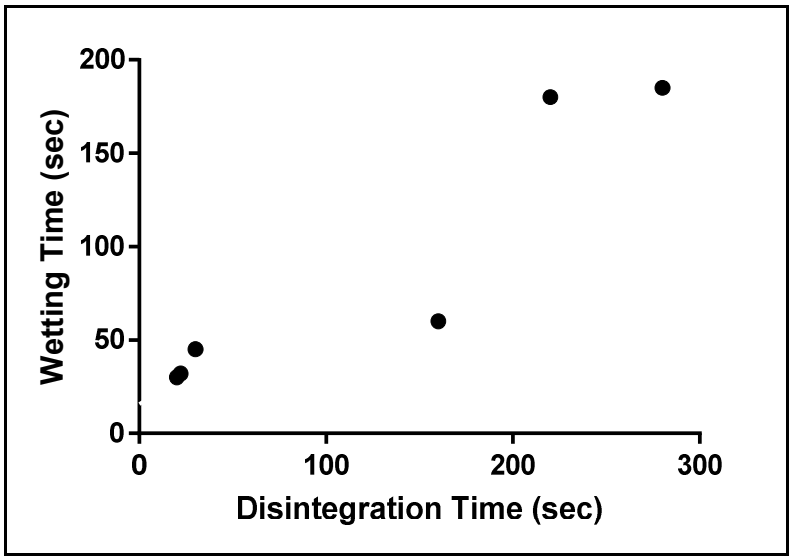

Figure 4: A scatterplot summarizes the results for Pearson product-moment correlation between wetting and disintegration times of the prepared orodispersible tablets of ABZ. Confidence interval = 95%

3.2.6. *In vitro* Dissolution test

Table 3 shows the results of the dissolution test for 30 minutes of ABZ formulations which was assigned as % drug release within time (min). Figure 5 demonstrates the release profile of the prepared formulas.

Table 3: Dissolution study of ABZ ODT formulations in 0.1N HCl expressed as present of drug release for 30 min

Time (min)	% drug release					
	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	40.12	50.22	26.78	13.45	5.53	65.35
2	41.98	52.94	27.56	15.52	6.39	66.13
5	43.43	53.08	28.92	15.58	8.75	66.50
10	45.00	67.25	35.00	35.25	32.50	73.67
15	54.67	68.25	71.25	51.58	47.50	75.00
20	58.42	73.66	74.00	60.25	60.50	76.58
25	65.50	74.92	75.50	67.58	61.17	75.58
30	67.33	75.83	77.25	72.75	61.83	75.92

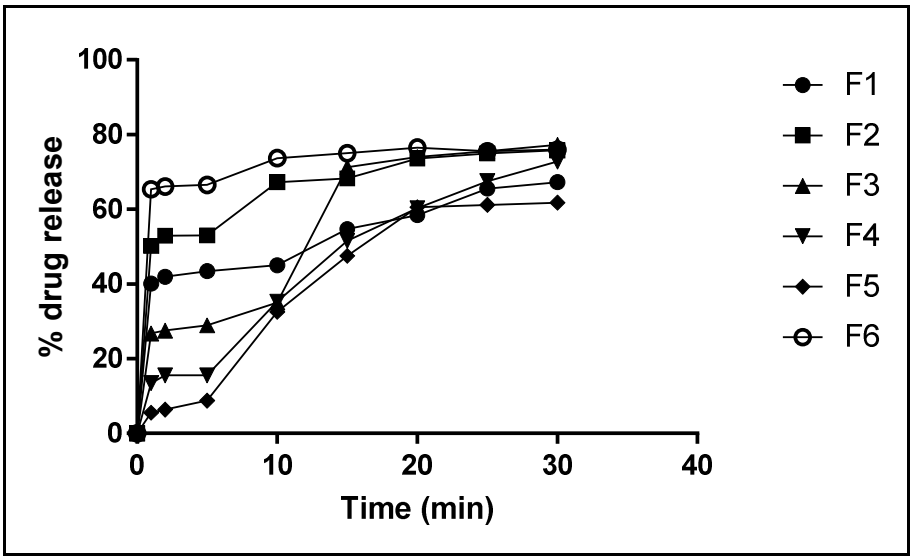

Figure 5: Dissolution test (% drug release within time) for F1-F6 of ABZ ODTs

4. DISCUSSION

Albendazole (which is an example of Class II drugs) was selected to be formulated as an orodispersible tablet because ODTs could be prepared for insoluble drugs if their dose is lower than 400 mg (16). Materials were selected of analytical grade to be of high purity for analytical study to reduce the effect of impurities on albendazole solubility. CCS, CP and banana were the selected disintegrating agents. The low effect of Mg St on tablet hardness and disintegration had made it the optimal lubricant to be used (17). Saccharin was added as a sweetening agent. Mannitol was selected as a diluent due to its cooling effect in the mouth and its free flowability (18). The purity of albendazole was confirmed by its measured melting point which was 208 ºC.

In addition to melting point, λmax of albendazole was referred to characterize the powder. Beer-Lambert`s law was obeyed since a straight line was obtained by plotting the absorbance versus the concentration during the determination of the calibration curve of albendazole. Six formulas were proposed and a simple and time and money preserving technique was selected to prepare the orodispersible tablets of albendazole through the application of direct compression method. Since tablets were compressed individually (by weighing the required total weight for each tablet) and a constant compression force was applied, post-compression physical parameters had fulfilled the stated values for an accepted orodispersible tablet.

It could be concluded from Table 2 that F2 (which contains 5% CCS) and F6 (which contains 40 mg (10%) CP) had the shortest wetting and disintegration times while F5 (which contains 5% of banana powder) had the longest. It was also noted that there was a direct relationship between the increment in the percentage of banana powder in the formulas and their wetting and disintegration times. This could be attributed to the fact that banana could work as a binder as well as a disintegrating agent (7). Additionally, the delayed disintegration times of

banana formulations could be attributed to the high content of albendazole which has poor water solubility.

The solubility of the tablet matrix could significantly affect the effectiveness of the superdisintegrant in promoting tablet disintegration. Hence, water uptake by the tablets to disintegrate is hindered (20). Although there was a strong positive correlation between wetting and disintegration times, correlation between disintegration and dissolution is unnecessary. F3 had a prolonged disintegration time but produced the highest % drug release among other formulations within the studied period which could be attributed to the fact that the disintegrated drug fragments may not release the drug itself (21).

Generally, a shorter disintegration time and higher % drug release was observed in CCS containing formulas (F1: 2.5% and F2: 5%) by increasing the amount of CCS. On the other hand, banana containing formulations (F3: 1.25%, F4: 2.5% and F5: 5%) had longer disintegration times and lower % drug release when the amount of banana was increased. This effect could be attributed to the formation of a concentrated barrier of the superdisintegrant during the disintegration step which then affected the dissolution process (18). Table 3 shows an abrupt increase in % drug release during (5-10) min dissolution test in formulas F1 and F2. However, no significant difference was found among the calculated values. About 52-75% of albendazole was released from the prepared ODT formulations regardless of the used superdisintegrating agent. On the other hand, no release was observed during the first 15 minutes of the dissolution study of pure and conventional albendazole tablets (23).

5. CONCLUSION

Orodispersible tablets of albendazole were prepared by direct compression method employing three superdisintegrating agents (sodium croscarmellose, crospovidone and banana powder). It have been demonstrated that the type and amount of superdisintegrant had a significant effect on the wetting and disintegration times and the % drug release of the prepared orodispersible tablets. Although formulations that contained banana powder (F3, F4 and F5) were unsuccessful as ODTs in disintegration test, their release profiles were successful when compared with conventional tablets. F6 which contained 10% crospovidone had the most acceptable *in vitro* evaluation studies followed by F2 that contained 5% croscarmellose.

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