Formulation and Evaluation of Palatable Orodispersible Tablets of Amoxicillin Trihydrate Suitable for Pediatric Use

[1]Nahla Sameh[*], [2,3]Ahmed Khames, [4]Sadia A. Tayel.

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Nahda University, Egypt.
[2] Faculty of Pharmacy, Beni-Suef University, Egypt,
[3]Department of Pharmaceutics and Pharmacy Technology, Faculty of Pharmacy, Taif University, Taif, KSA,
[4]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Egypt.
sokar1100@yahoo.com

Abstract: Objective: To formulate orally disintegrating tablets (ODT) of Amoxicillin Trihydrate (AMT) suitable for pediatric use to combine the advantages of easy use, accurate dosing in a stable dosage form. **Method:** ODT were prepared by direct compression using Ac-Di-Sol, Sodium starch glycolate, Polyplasdone and Pharmaburst as superdisintegrants at different concentrations. Mannitol was added as diluent in all prepared ODT formulae except Pharmaburst based formula. The prepared tablets were evaluated for drug content, weight variation, hardness, friability, water absorption rate, and wetting time. In vitro/vivo disintegration time was estimated. In-vitro dissolution behavior of AMT from the prepared ODT at both salivary and gastric conditions was investigated. Finally; taste evaluation of the prepared ODTs was applied on healthy human volunteers. **Result:** All formulation blends showed good flow properties, uniform thickness, diameter, weight and good mechanical resistance and breaking strength. The wetting time was in the range of 90 to 43sec and absorption ratio range from 120.71 to 153.4. Polyplasdone and Pharmaburst based ODT formulae showed the shortest disintegrating time (44 and 45 sec respectively), disintegration in buccal cavity was between 22 and 60sec. Regarding dissolution results, F8 and F10 showed the highest dissolution rate (66.35% and 67.97% respectively) within 30 minutes in phosphate buffer pH 6.8. In 0.1N HCl, the percentage of drug released was more than 85% within 30 minutes from all prepared ODT formulae. Formulae 8, 9 and 10 showed the highest dissolution (AMT released reached 100% within 15 minutes). **Conclusion:** Depending on the previous results it can be concluded that the proposed ODT formulae of AMT are suitable and efficient substituent for the commonly marketed suspension for pediatric use.
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1. Introduction:

Orally disintegrating tablets help a patient who suffers from swallowing difficulties which is reported to be common among different age group especially pediatric and geriatric patients, also patients suffer from nausea, vomiting or motion sickness complications. It is important for orodispersible tablets to be palatable to mask any bitter taste of drug and to increase its acceptability by all groups of patient. [1]

These dosage forms are intended to disintegrate and/or dissolve in saliva upon placing in the mouth without water, after disintegration occurs in buccal cavity the drug is released [2].

Amoxicillin (a penicillin antibiotic), is used as first line treatment for different infections caused by bacteria, such as ear, nose and throat infections, bladder infections, pneumonia, gonorrhea, and *E. coli* or salmonella infection. This drug acts by inhibiting the synthesis of bacterial cell walls. It inhibits cross linkage between the linear peptidoglycan polymer chains that make up a major component of the cell walls of both Gram-positive and Gram- negative bacteria. It has two ionizable groups in the physiological range. (the amino group in alpha-position to the amide carbonyl group and the carboxyl group)[3]

Amoxicillin is 80% absorbed from oral route with a good efficacy and safety [2].

The objective of this study was to formulate an Amoxicillin orodispersible tablet with low disintegration time, acceptable taste and good drug release profile suitable for pediatric patients.

2. Material and Methods

2.1. Materials:

Amoxicillin Trihydrate (AMT), Mannitol, Polyplasdone, Magnesium Stearate, Pharmaburst, Sodium starch glycolate, Ac-Di-Sol, Aspartame and Orange flavor were received as gift samples from EPCI, Beni-Suef, Egypt. Disodium hydrogen phosphate, potassium dihydrogen orthophophosphate (Sigma-Aldrich, Germany). All other ingredients used throughout the study were of analytical grades and were used as received.

2.2. Methods:

2.2.1. Preparation of orodispersible tablets of AMT:

Each tablet containing 292 mg AMT was prepared as per composition given in Table (1). Before compression, the previously sieved drug, diluent and disintegrant were mixed in geometrical order in glass mortar, and then passed through sieve No. 60 to ensure the better mixing, followed by tumbling for 15 minutes, then the lubricant was added and mixing was continued for further five minutes. In this work; Ac-di-Sol, sodium starch glycolate, Polyplasdone and Pharmaburst were used as super disintegrants in different ratios; Mannitol was used as a direct compressible vehicle in all proposed ODT formulae except Pharmaburst based one because Pharmaburst is certified to be used as direct compressible vehicle of superdisintegrantion characteristics. The prepared powder mixtures were directly compressed using Single Punch Tablet Press (TDP, SHANGHAI TIANHE, Pharmaceutical machinery factory, China). equipped with 12 mm round punch to give 450mg weight tablet [4]. Ten ODT formulations were prepared. 50 tablet batch of each formula was prepared and subjected to further evaluation.

2.2.2. Evaluation of the prepared orodispersible tablet formulae:

The prepared ODT formula mixtures were evaluated on two levels as following:

Pre Compression Evaluation: (Determination of flow and compression properties):

The flow and compression properties of the prepared ODT formula mixtures were determined by measuring:

a) Angle of repose

The repose angle (θ) of the prepared formulation powders was determined using fixed funnel method [5]. The blend was allowed to freely flow through a funnel that was suspended vertically at a height (h) of the cone tip. Radius of the formed heap (r) was measured. Each experiment was run in triplicates and angle of repose was calculated using the following equation:

$\theta = Tan^{-1} h/r$

b) Bulk density and Tapped density

Five grams of each of the prepared ODT formula powders were weighed and poured into a tarred graduated cylinder. The cylinder was then dropped from a height of 1 inch onto a hard surface three times at 2-seconds intervals. The volume occupied was then recorded as the bulk volume (V_b). The cylinder was tapped till constant volume and the obtained volume was recorded as the tapped volume (V_t). The process was repeated three times and the average was taken in each case [6].

The bulk and tapped densities of the formulations powders were calculated by dividing the weight by the corresponding bulk or tapped volume recorded according to the following equations:

$\rho_b = M/V_b$ $\rho_t = M/V_t$

Depending on the calculated bulk and tapped densities, Hausner's ratio and Compressibility (Carr's index) were as follows:

c) Hausner's ratio [7]

Calculated using this equation:

Hausner's ratio = Tapped density/Bulk density

d) Compressibility index (Carr's index) [8]

Calculated using this equation:

Carr's index (%) = (Tapped density – Bulk density)/ (Tapped density) X 100

Post Compression Evaluation (Evaluation of the prepared ATODT)**:**

The prepared ODT were subjected to the following evaluation tests:

1. **Weight variation** [9]

Twenty tablets were selected at a random and average weight was calculated. Then the individual tablet weight was calculated and compared with the average weight.

2. **Uniformity of ODTs thickness and diameter** [10]

The diameter and thickness of ten tablets were measured using Valiner caliber at two different positions. The average value was then calculated.

3. **Uniformity of AT content in the prepared tablets** [11]

Ten tablets were used in this test, where each one was separately crushed and transferred into 100 ml volumetric flask. The flasks were brought to volume by phosphate buffer pH 6.8.The flasks were placed onto a sonicator till complete dissolution, 1ml of the solution was filtered through a 0.45 µm pore size filter then introduced into 25 ml volumetric flask which was completed to volume by phosphate buffer. The absorbance of the solution was spectrophotometrically determined at 228 nm which was previously determined as wavelength of maximum absorption (λmax). The tablets meet the test if the mean drug content lies within the range of 85-115% of the labeled potency.

4. **Tablet hardness** [12, 13]

Ten tablets from each formula were subjected this test, using a tablet Hardness Tester (DR-SCHLENGER Pharmaton, 6D, USA). The average of applied pressure (kg/cm^2) for crushing the tablet was determined.

5. **Friability test** [12, 13]

A sample of accurately weighing 20 tablets of each formula was placed in the drum of friabilator. They were rotated at 25 r.p.m for a period of four minutes (i.e., 100 rotations). The tablets were removed, brushed, reweighed and the percentage loss in the weights was calculated and then taken as a measure of friability.

The percent friability was determined by using following formula:

% friability = (initial weight- final weight) x 100 Initial weight

6. Wetting time and water absorption ratio: [14, 15]

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 ml of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Tablets were separately weighed (W_a) and carefully placed onto the surface of a piece of tissue paper twice folded in a 5 cm diameter petri dish containing 6 ml of aqueous amaranth solution. The time (in seconds) for complete wetting (water reaches the upper surface of the tablet) was noted and recorded as the wetting time. The wetted tablet was carefully removed and reweighed (W_b)

Water absorption ratio (R) through the tablet was then determined according to the following equation: $R= (W_a – W_b)/ W_b \times 100$

7. In-vitro disintegration time [16]

In vitro Disintegration time: The disintegration time for all formulations was carried out using tablet disintegration test apparatus containg distilled water (PH= 6.8) at 37±0.5ºC as disintegration medium. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The time taken for the entire tablet to disintegrate completely was noted as the disintegration time.

8. In –vitro dissolution studies:

Science the ODT is intended to disintegrate in saliva before swallowing dissolution in salivary fluid is to be considered so; the dissolution test was carried out both in salivary (phosphate buffer, pH 6.8) and gastric (0.1 N HCl, pH 1.2) media to study the expected drug release in both mouth and stomach.

In vitro drug release studies of all the formulations were carried out using USP Dissolution tester type II (Hanson Research, SR 8 Plus model, Chatsworth, USA) at 75 rpm. This test was carried out in 0.1 N HCl- pH 1.2 and phosphate buffer- pH 6.8 media to study the drug release in both mouth and stomach. Temperature was maintained at 37±1ºC.

Samples were withdrawn at predetermined time intervals (5,10,15,25,30 and 45 minutes in 0.1N HCl) and (1,3,5,7,10,15,20,25 and 30 minutes in phosphate buffer) and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Samples were diluted suitably and analyzed at 224nm and 228 nm in 0.1N HCl and phosphate buffer respectively for cumulative drug release using UV-VIS Ultraviolet spectrophotometer (Jasko, V-530, Japan).

Dissolution study for AMT ODT formulation was done in comparison to dissolution study for Amoxicillin 250mg capsule (Hiconcil 250 mg capsule) from the Egyptian market [3].

9. *In- vivo* disintegration time in the buccal cavity:

The disintegration time of ODTs was measured in sixteen healthy male volunteers (22–37 years old). The disintegration test in the oral cavity was assessed according to the method described by Ogata *et al.* [17]. The volunteers were informed about the protocol and purpose of the study; all were asked to rinse their oral cavity with water prior to the test. Each volunteer was asked to place one tablet on the tongue and close the mouth; a stopwatch was started immediately. The end point of disintegration in the human sensory test was defined as the time when the tablet placed on the tongue had disintegrated without leaving any lumps. All the volunteers were instructed to rinse their mouth after completion of the test. This study was performed in accordance with the regulations of the Declaration of Helsinki about research in humans[18].

10. Assessment of the taste of the ODTs of the best formulae [19]

Taste evaluation was done using time intensity method on six healthy volunteers. One ODT of each formula was held in the mouth until complete disintegration. Bitterness was recorded immediately and at several intervals for one minute (10 seconds, 20 seconds and 60 seconds) according to the bitterness intensity scale from 0 to 3 where 0 = tasteless, 0.5 =after taste, 1.0 = slight, 1.5 = slight to moderate, 2.0 = moderate, 2.5 = moderate to strong, 3 = strong and 3^+ = very strong.

3. Results and discussion

In this work; AMT was blended with different superdisintegrants types (namely Ac-di-Sol, sodium starch glycolate, Polyplasdone and Pharmaburst) at different concentration to prepare palatable rapidly disintegrating tablets. According to formula Table 1, ten ODT formulae of AT were prepared and evaluated.

The flow properties of the proposed ODT formula mixtures were evaluated depending on angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio values. As a general guide, powders with angles of repose greater than 40° have unsatisfactory, extremely poor flow properties, whereas powders with angles of repose less than 30° correspond to very good flow properties, powders with (θ) up to 35° have passable flowability, and those having (θ) between 35° and 40° suggest that the powder flows with difficulty and may be improved by addition of glidant. [20, 21]

According to results listed in Table 2 and graphically presented in figure 1, values for angle of

repose were found in the range of 20.13° to 28.56° showing that the blend of powder has very good free flowing and can be used for direct compression. The bulk density was found to be within range 0.20 to 0.29 while tapped density was 0.26 to 0.32. The value for Carr's index was in between 11.96 to 15.79 indicating that most batches of powder blends were having good or fair compressibility. Hausner's ratio was found to be within limits (<1.25). All formulation blends showed good flow properties and this is mainly attributed to the excellent flow characteristics of used superdisintegrants hence tablets were prepared by direct compression method.

Results of physical characterization of the prepared ODT are shown in Table (3). According to these results, all the prepared tablets are characterized by a uniform thickness, diameter and weight indicating efficient mixing. The weight variation of all the tablets was within the ranges of 448.8 – 452.2mg. The thickness of the tablets was within the range of 4.00 – 4.12mm; while the diameter was found to be between 9.38 and 9.66. All formulation passes the drug content assay. Uniformity of drug contents was within range 96.9 and 99.4%. All formulations showed good mechanical resistance and breaking strength, where the hardness of the tablets was within the range of 5.11-6.68 Kg/cm^2. The friability of all tablets below 1% except Starch sodium Formula F5 was friable and showed percentage weight loss that exceeded pharmacopeial limits (1.63%) due to capping.

The behavior of the prepared ODT in contact with water was studied by measuring wetting time, water absorption rate, in vitro/ in vivo disintegration time, and drug release rate. Depending on the results showed in Table 4, it was observed that as the concentration of superdisintegrants is increased Figure 2, time taken for wetting was reduced and the wetting time of all the formulated tablets was in the range of 90 ± 2.08 to 43 ± 1.33 seconds.

Water absorption ratio 'R' increased with an increase in superdisintegrants' concentrations. The increase in 'R' was most likely due to increased water uptake capacity of the superdisintegrants at higher concentrations.Water absorption ratio for AMT ODT formulations range from 120.71 to 153.4. Wetting time is used as an indicator of the ease of tablet disintegration in buccal cavity which was found to be between 22 and 60sec.

F4 and F5 had the longest average in vitro disintegration time of 165 seconds and 140 seconds respectively, while F8 and F10 had the shortest average in- vitro disintegration time of 44 seconds and 45 seconds respectively.

Results of the dissolution test of AMT ODT are graphically illustrated in figures (3-11). Dissolution test was carried out in both phosphate buffer pH 6.8 and 0.1N HCL. The extent of dissolution of AMT from the commercial product Hiconcil 250mg reached 98.4% after 45 minutes.

In 0.1N HCl media: All prepared ODT formulae showed acceptable dissolution rate, where more than 85% of the labeled dose was dissolved within 30 minutes which complies with the USP pharmacopeial limits. Formulae 8, 9 and 10 showed the highest dissolution where the percentage of AMT released reached 100% of the labeled dose within 15 minutes and this could be correlated to the highly hydrophilic and superdisintegrantion power of Polyplasdone and Pharmaburst.

In phosphate buffer pH 6.8: F8 and F10 showed the highest dissolution where 66.35% and 67.97% of the labeled dose was dissolved from both formulae respectively within 30 minutes.

Table (5) reveals the taste evaluation results of AMT ODTs. The bitterness scale for F10 ranged from 0 (no bitterness) at 10 seconds and 20 seconds to 0.5 (threshold bitterness) at 60 seconds, while the bitterness scale for formulae (F1 to F 9) ranged from 0 (no bitterness) at 10 seconds to 0.5 (threshold bitterness) at 20 seconds to 1 (slight bitterness) at 60 seconds. Sensory evaluation of the selected ODTs proved good palatability [22].

Table (1): Formula composition of the proposed AT ODTs.

Formula No.	Drug	Disintegrant Type	Disintegrant Ratio	Lubricant	Flavor	Diluent (Mannitol)
1	Amoxicillin Trihydrate (292 mg)	Ac-Di-Sol	4% (18 mg)	Magnesium stearate (4.5 mg)	Orange flavor (4.5 mg) Aspartame (4.5mg)	126.5 mg
2			6.5% (30mg)			114.5mg
3			8% (36 mg)			108.5mg
4		SSG	4% (18 mg)			126.5 mg
5			6.5% (30mg)			114.5mg
6			8% (36 mg)			108.5mg
7		Polyplasdone	4% (18 mg)			126.5 mg
8			6.5% (30mg)			114.5mg
9			8% (36 mg)			108.5mg
10		Pharmaburst	32.1% (144.5mg)			-

Table (2): Flowability parameters of the prepared powder formulations:

Formula No.	Angle of repose	Bulk density	Tapped density	Hausner's ratio	Carr's index
AMT	34.73	0.35	0.46	1.26	30.98
F1	28.35	0.27	0.26	1.16	14.80
F2	28.56	0.29	0.27	1.20	15.79
F3	28.40	0.25	0.27	1.23	15.24
F4	27.56	0.24	0.27	1.22	14.34
F5	27.38	0.29	0.30	1.23	13.67
F6	27.80	0.29	0.30	1.11	13.67
F7	25.30	0.25	0.28	1.10	12.79
F8	25.60	0.29	0.30	1.09	12.30
F9	25.85	0.21	0.32	1.01	12.65
F10	20.13	0.20	0.26	1.01	11.96

Table (3): Evaluation of the prepared AMT orodispersible tablets

Formula code	Weight* variation ±SD	Diameter (mm) ± S.D	Thickness (mm) ± S.D	Drug content (%) ± S.D	Hardness (Kg/cm^2± S.D)	Friability %))
F1	449 ±0.60	9.40 ± 0.003	4.02 ±0.03	98.9±1.02	6.25 ±0.12	0.2
F2	450.3 ±0.18	9.42 ± 0.001	4.11 ±0.04	98.2±1.25	6.28 ±0.20	0.18
F3	451.1 ±1.9	9.58 ± 0.016	4.09 ±0.02	96.9±0.94	6.31 ±0.18	0.13
F4	452 ±0.80	9.66 ± 0.005	4.05 ±0.03	97.8±0.98	5.11 ±0.15	0.58
F5	450.9 ±1.88	9.57 ± 0.008	4.12 ±0.02	98.5±1.05	5.20 ±0.38	1.63**
F6	449 ±0.78	9.49± 0.012	4.02 ±0.03	99.1±1.06	5.16 ±0.23	0.54
F7	448.8 ±1.12	9.38 ± 0.009	4.00 ±0.02	99.4±0.89	5.38 ±0.19	0.26
F8	452.2 ±1.08	9.40 ± 0.016	4.03 ±0.03	97.9±1.02	5.44 ±0.14	0.24
F9	451.3 ±0.98	9.51 ± 0.003	4.11 ±0.04	98.9±1.22	5.67 ±0.27	0.24
F10	450.3 ±1.80	9.52 ± 0.003	4.09 ±0.03	98.2±1.09	6.68 ±0.13	0.12

*All values are expressed as mean ±SD, n=3 **capping

Table (4): Characterization of hydrophilic properties of AMT orodispersible tablets

Formula code	Avg. wetting time* (Sec) ± SD	Avg. Water Absorption* (%) ±SD	In-vivo disintegration time (Sec) ± S.D	In-vitro disintegration time (Sec) ± S.D
F1	90.00±2.08	145.3±0.68	35 ±3.55	70 ±0.57
F2	82.00 ±1.99	149.9 ±0.75	30 ±4.05	55 ±0.63
F3	65.00 ±1.89	153.4 ±1.04	22 ±3.85	49 ±0.61
F4	89.00 ±2.14	126.5 ±0.35	60 ±3.76	165 ±1.25
F5	71.00 ±2.35	131.6 ±0.21	53 ±4.12	140 ±1.55
F6	59.00 ±2.14	139.71 ±0.63	48 ±6.12	116 ±1.55
F7	67.00 ±1.63	130.7 ±0.42	23 ±5.64	48 ±0.74
F8	54.00 ±1.54	128.3 ±0.33	25 ±5.03	44 ± 0.95
F9	43.00 ±1.33	144.6 ±0.71	27 ±3.44	52 ±1.02
F10	52.00 ±0.81	120.71 ±0.63	29 ±3.56	45±1.40

*All values are expressed as mean ±SD, n=3

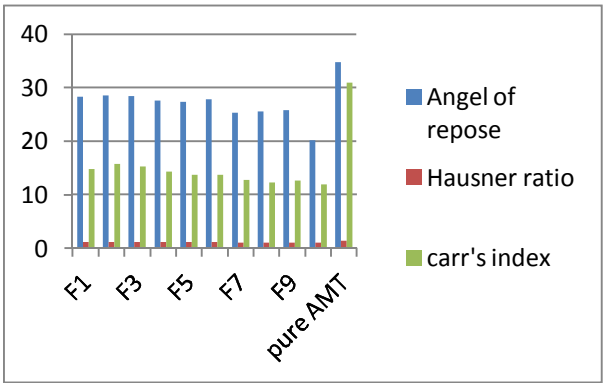

Figure (1): Histogram of Angle of repose, Carr's index and Hausner's ratio of AMT and its prepared ODT formulae

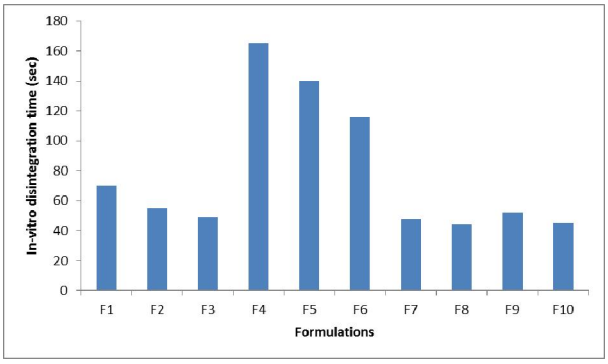

Figure (2): In-vitro disintegration profile of the prepared ODT formulations.

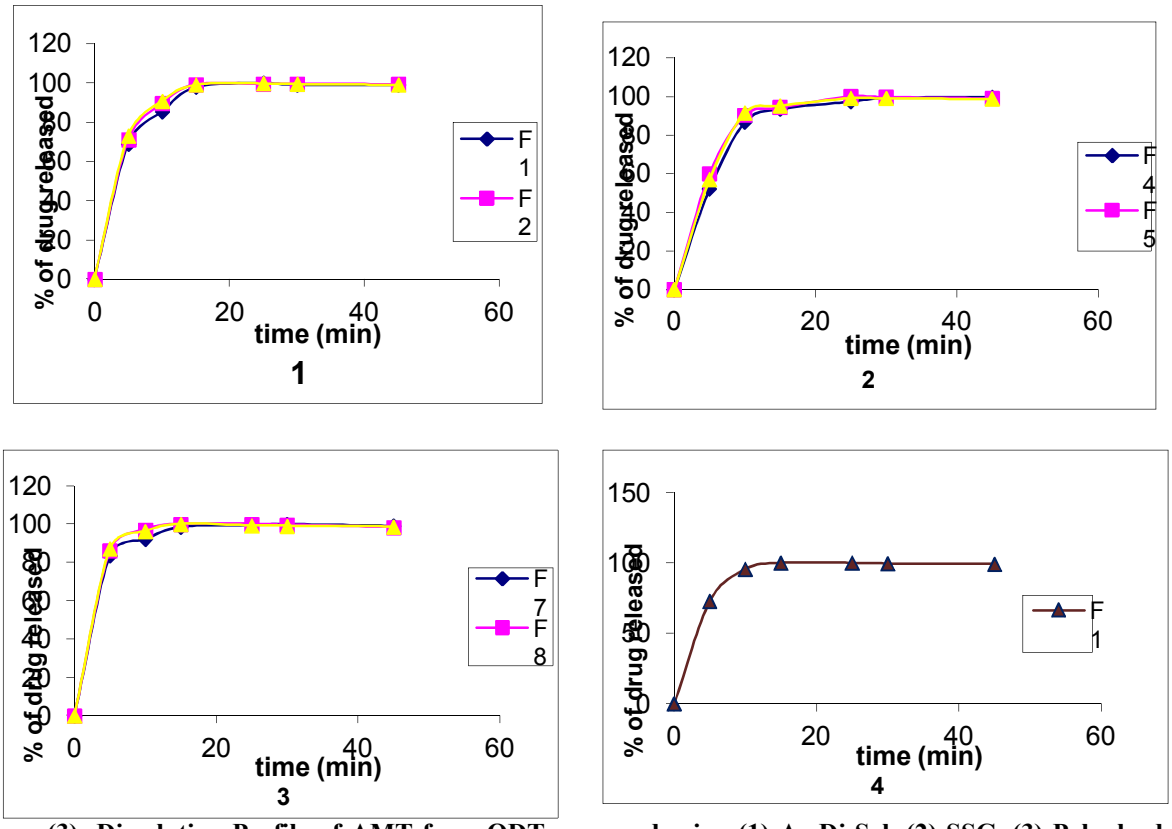

Figure (3): Dissolution Profile of AMT from ODT prepared using (1) Ac-Di-Sol, (2) SSG, (3) Polyplasdone, and (4) Pharmaburst as superdisintegrants in 0.1 HCl

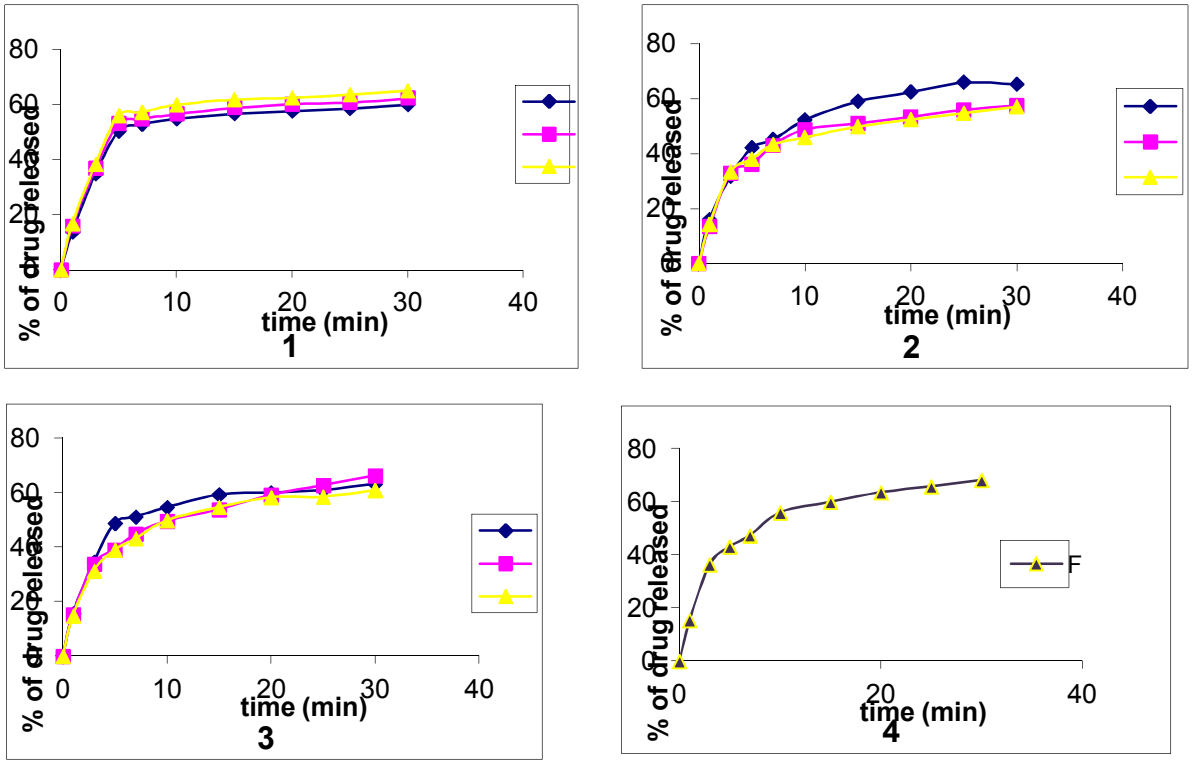

Figure (4): Dissolution Profile of AMT from ODT prepared using (1) Ac-Di-Sol, (2) SSG, (3) Polyplasdone, and (4) Pharmaburst as superdisintegrants in phosphate buffer pH 6.8.

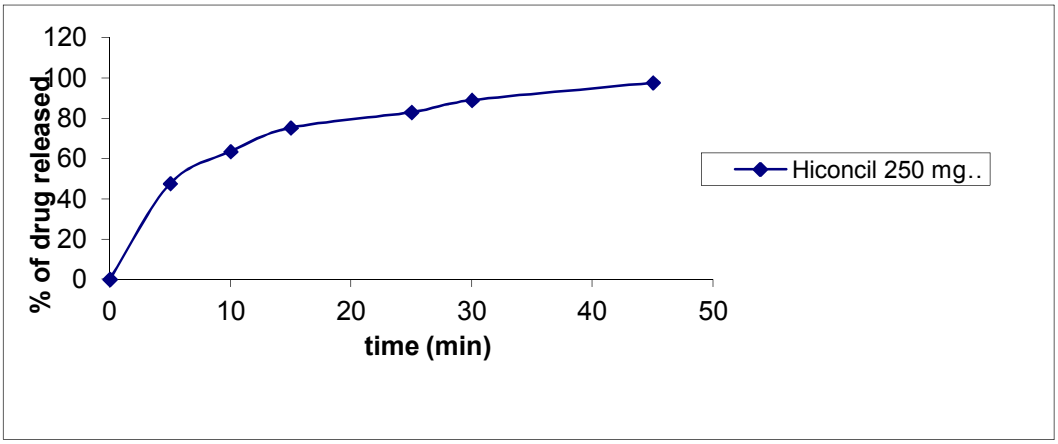

Figure (5): In-vitro dissolution profile of Hiconcil 250mg capsule in simulated 0.1N HCl

Table (5): Taste evaluation of the AMT orodispersible tablets

Formula Code	Degree of bitterness after time (Sec)		
	10	20	60
F1	0	0.5	1
F2	0	0.5	1
F3	0	0.5	1
F4	0	0.5	1
F5	0	0.5	1
F6	0	0.5	1
F7	0	0.5	1
F8	0	0.5	1
F9	0	0.5	1
F10	0	0	0.5

4. Conclusion

Depending on the results of the study it can be concluded that; the proposed superdisintegrants in the applied concentrations were suitable for the preparation of palatable orodispersible tablet formulations containing amoxicillin trihydrate simply by direct compression. The proposed formulae showed good compression, wetting, disintegration, and release properties. So we recommend the proposed formulae as an efficient substitute for the marketed suspension of better stability, palatable taste and more economic value.

Corresponding Author
Nahla Sameh
Address: Department of Pharmaceutics, Faculty of Pharmacy, Nahda University, Beni suef, Egypt.
Email: sokar1100@yahoo.com

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