Preparation of a New Dosage Form of Metoclopramide Hydrochloride as Orodispersible Tablet[#]

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Abstract

Metoclopramide HCl (MTB) is a potent antiemetic drug used for the treatment of nausea and vomiting. Many trials were made to prepare a satisfactory MTB orodispersible tablet using direct compression method.Various super disintegrants were used in this study which are croscarmellose sodium (CCS), sodium starch glycolate (SSG) and crospovidone (CP). The latter was the best in terms of showing the fastest disintegration time in the mouth.Among the different diluents utilized, it was found that a combination of microcrystalline cellulose PH101 (MCC 101), mannitol, dicalcium phosphate dihydrate (DPD) and Glycine was the best in preparing MTB orodispersible tablet with fastest disintegration time in the mouth.The physical parameters of the prepared MTB orodispersible tablet were satisfactory as hardness (4 Kg), friability (0.5%) and mouth disintegration (23 sec).The overall results suggest that the prepared formula of MTB as orodispersible tablet could be utilized as a new dosage form for the oral administration.

Key words: Orodispersible, metoclopramide, super disintegrant

الخلاصة

يعد عقار الميتوكلوبراميد هايدروكلوريد (Metoclopramide HCl) من العقارات الفعالة في علاج حالات التقيؤ. هذه الدراسة تتعلق بتصنيع الميتوكلوبراميد هايدروكلوريد على شكل حبة سريعة التحلل في الفم (orodispersible tablet) باستخدام طريقة الكبس المباشر.تم استخدام عدة مواد مفككة وهي مادة (croscarmellose sodium) ومادة (sodium starch glycolate) ومادة (crospovidone). ويعد الأخير هو الأفضل لأن وقت تحلله في الفم كان اسرع من باقي المواد المفككة. من بين مواد التخفيف المستخدمة، وجد بأن مادة السليلوز مجهري التبلور والمانيتول ومادة (dicalcium phosphate dihydrate) والكلايسين كانت هي الافضل في تصنيع حبة الميتوكلوبراميد هايدروكلوريد سريعة التحلل في الفم. وكانت الخصائص الفيزيائية لحبة الميتوكلوبراميد هايدروكلوريد سريعة التحلل في الفم جيدة فمثلا كانت صلابة الحبة ٤ كغم في حين كانت الهشاشة ٠,٥% اما وقت التحلل في الفم فهو ٢٣ ثانية.

Introduction

Orodispersible tablet is a solid dosage form containing a medicinal substance that disintegrates and/or dissolves rapidly in the mouth (either on or beneath the tongue or in the buccal cavity) without drinking water within up to three minutes. Upon placement in the mouth, orodispersible tablets absorb saliva rapidly into the tablet core allowing the super disintegrant to swell, rupture the tablet and liberate the individual components that form solution or suspension, which in turn can be swallowed easily without water. On the other hand, orodispersible tablet can also be swallowed intact as it is; i.e., as if it was a conventional tablet by using water to push it down to stomach [(1)].The orodispersible tablets have increased in popularity because consumers, all ages, find them convenient and easy to use. Since orodispersible tablets can be taken without water, therefore, bed-ridden, lying, standing, walking, talking, and traveling patients can use them easily any time and anywhere [(2)].Orodispersible tablet is the proper solution for dysphagia. Dysphagia is defined as difficulty swallowing food or liquids, which may be caused by normal physiologic response or as a result of disease state[(3)]. As a consequence of dysphagia, children and elderly patients do not take their medication as prescribed. It is estimated that as high as 50% of the population has this problem which results in a high prevalence of ineffective therapy [(4)].Other advantage of orodispersible tablets is fastening onset of action. They disintegrate in the mouth in a period of seconds in comparison to conventional tablets which may need up to 15 min to disintegrate completely in the stomach. Furthermore, a dissolution process for water-soluble drugs begins to initiate while the orodispersible tablet still in the mouth. These facts reflect why orodispersible tablets have rapid or ultra rapid onset of action [(5)].

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Many side effects are associated with the conventional dosage forms such as tablets and capsules. For example, these dosage forms may lodge esophagus, causing local irritation. When the tablet or capsule disintegrates in stomach, it may release all of its content in the same area, which may cause a gastric irritation especially if the drug is highly water soluble due to the formation of localized high concentration. Regarding orodispersible tablet, it disintegrates and/or dissolves in the mouth and diluted subsequently with saliva, so no such side effect can take place.According to the above advantages, orodispersible tablets can be used for most cases, but their benefits can be doubled in certain clinical situations; among them are nausea and vomiting. During nausea and vomiting, it is better for the patient to take orodispersible tablet and not a conventional one due to the following reasons[6]:

a. To avoid the stimulation of vomiting center in the CNS. This center is stimulated by GI distention which, in turn, is caused by food or fluid intake. If the patient takes conventional tablet, he should use a glass of water to swallow it and hence, vomiting reflux may be initiated, bringing about a new vomiting episode.

b. Physiologic defense mechanism which makes the patient reluctant to drink.

Many products of orodispersible tablets have been launched worldwide over the past decade by the most famous drug companies. AstraZeneca, GlaxoSmithKlin, Eli Lilly, Pfizer, Wyeth, Squibb, Bristol-Myers, Schering Plough, Merck, Janssen and Organon are examples on these companies [7].

Experimental Materials:

The following materials were used in this study: CCS and CP (Al-Hekma Drug Industry, Jordan), MTB, SSG and DPD (Samara Drug Industry (SDI), Iraq), lactose, mannitol and hydrochloric acid (HCl) (Riedal De Haen Ag Seelze Hanover, Germany), glycine (Fluka Chemi Ag, Switzerland), magnesium stearate (Mg St) (Barbeher, GmbH, Germany), Meclodin® tablet (SDI, Iraq), Primperan® tablet (Sanofi corp., France).

Methods:

Formulation of Orodispersible Tablet:

Formulation of Control Orodispersible Tablets (without MTB):

Different control formulas (without MTB) were prepared and tested to obtain the best formula that disintegrates as fast as possible in the mouth (table 1). 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 3 min. The final mixture was compressed using a double punch, Korsch, tablet machine with a 10 mm flat punch.

Formulation of MTB Orodispersible Tablet:

MTB was incorporated with the best control formula (with regard to shortest disintegration time in the mouth) to obtain the final MTB orodispersible tablet that subjected subsequently to further investigations. The MTB orodispersible tablet was prepared by the same method mentioned above.

Physical Parameters Measurement of the Prepared Orodispersible Tablets:

Content Uniformity:

this test was undergone for the prepared MTB orodispersible tablet. The content uniformity was performed by taking ten tablets and assayed individually. The requirement for this test is met if the amount of ingredient in each of the ten tablets lies within the range of 85-115% of the label claim [8].

Hardness:

the hardness of all the prepared orodispersible tablets (with and without MTB) were measured using Monsanto hardness tester. Results are expressed as a mean ± S.D (n=3).

Friability:

the friability test was undergone for the prepared MTB orodispersible tablet using Roche friabilator for 4 min at 25 r.p.m. by taking ten tablets weighing them all together then placing them inside the tester. After their revolution, they were cleaned from dust and weighed again. The friability was calculated as the percent weight loss. If the reduction in the total mass of the tablets is more than 1%, the tablets fail the friability test [8].

Disintegration Test:

Two types of disintegration tests were done for the prepared orodispersible tablets: by using the disintegration apparatus (in vitro test) and disintegration test in the mouth using healthy volunteers (in vivo test).

Conventional Disintegration Test (in vitro test):

the disintegration time of the prepared MTB orodispersible tablet was determined in different solutions (D.W, 0.1N HCl pH 1.2 and phosphate buffer pH 6.5). In addition, the disintegration time in D.W was determined for Meclodin® and Primperan® tablets as

references. Disintegration apparatus with a ended tubes and 10-mesh screen on the bottom was used. A tablet was placed in each tube of the basket and the time for complete disintegration of the six tablets was recorded[8].

***Disintegration Test in the Mouth (in vivo test)**:*

Five healthy volunteers were subjected to the measurement of the disintegration time in the mouth of all the prepared orodispersible tablets (with and without MTB). Prior to the test, all volunteers got a detailed briefing on purpose of this test, then they were asked to rinse their mouth with water. Then the prepared orodispersible tablet was placed on the tongue and immediately a stopwatch was started. They were allowed to move the orodispersible tablet against the upper palate of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side. Immediately after the last noticeable granule or fragment had disintegrated, the stopwatch was stopped and the time was recorded. The swallowing of saliva was prohibited during the test, and also saliva was rinsed from the mouth after each measurement. To check reproducibility, each volunteer repeated the test three times [9].

***Dissolution Test**:*

the basket method was used to determine the release profile of the drug from the prepared MTB orodispersible tablet. The test was carried out in three different dissolution media which are 900 ml of D.W, 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.5) at 37 ± 0.5 ^{0}C with constant stirring speed of 50 r.p.m for 30 min. In addition, the release profiles of basket rack assembly containing six open-the Meclodin® and Primperan® tablets (as references) were also determined using 900 ml of D.W at the same test environments. At preset time intervals, 5 ml samples were withdrawn and the filtrate was refluxed back using 5 ml of fresh dissolution medium. Samples were filtered through microfilter and analyzed spectrophotometrically at the λmax of MTB [8].

Factors Affecting Formulation:

Effect of Super Disintegrants Types and Concentrations on the Disintegration Time in the Mouth of the Prepared Control Orodispersible Tablets:

Formulas 1-12 (table 1) were utilized to study the effect of super disintegrant type (SSG, CCS and CP) and concentration (4, 8.5, 18 and 40 mg/tablet) on the disintegration time in the mouth of the prepared control orodispersible tablets. Formulas 14-16 were prepared to reveal the effect of super disintegrants combination at three different concentrations (1.65, 4.4 and 9.5 mg/tablet) on the disintegration time in the mouth of the prepared control tablets.

Effect of Diluents Types and Concentrations on the Disintegration Time in the Mouth of the Prepared Control Orodispersible Tablets:

Formulas 17-32 (table 1) were utilized to check the effect of diluent type (MCC101, MCC102, mannitol, lactose, L-HPC, DPD and glycine) alone and as combination of them at different concentrations on the disintegration time in the mouth of the prepared control orodispersible tablets.

Table (1): Composition of the Control Orodispersible Formulas

Material (mg) / Formula	SSG	CCS	CP	MCC 101	MCC 102	Mannitol	Lactose	L -HPC	DPD	Glycine	Mg St	Total Weight (mg)
1	4 *(2.5%)*			159							1	164
2	8.5 *(5%)*			159							1	168.5
Table (1): Continued.												

Material (mg) / Formula	SSG	CCS	CP	MCC 101	MCC 102	Mannitol	Lactose	L -HPC	DPD	Glycine	Mg St	Total Weight (mg)
3	18 *(10%)*			159							1	178
4	40 *(20%)*			159							1	200
5		4 *(2.5%)*		159							1	164
6		8.5 *(5%)*		159							1	168.5
7		18 *(10%)*		159							1	178
8		40 *(20%)*		159							1	200
9			4 *(2.5%)*	159							1	164
10			8.5 *(5%)*	159							1	168.5
11			18 *(10%)*	159							1	178
12			40 *(20%)*	159							1	200
13			54 *(25%)*	159							1	214
14	1.65 *(1%)*	1.65 *(1%)*	1.65 *(1%)*	159							1	164.95
15	4.4 *(2.5%)*	4.4 *(2.5%)*	4.4 *(2.5%)*	159							1	173.2
16	9.5 *(5%)*	9.5 *(5%)*	9.5 *(5%)*	159							1	188.5
17			40		159						1	200
18			40			159					1	200

Table (1): Continued

Material (mg) / Formula	SSG	CCS	CP	MCC 101	MCC 102	Mannitol	Lactose	L -HPC	DPD	Glycine	Mg St	Total Weight (mg)
19			40				159				1	200
19			40				159				1	200
20			40	80	79						1	200
21			40	80		69	10				1	200
22			40	80		79					1	200
23			40	59		100					1	200
24			40	40		120					1	201
25			40	20		140					1	201
26			40	20		140		2			1	203
27			40	20		140		23			1	224
28			40	20		140		50			1	251
29			40	20		140			11		1	212
30			40	20		140			23		1	224
31			40	20		140			50		1	251
32			40	20		140			23	55	1	279

Effect of pH on Conventional Disintegration Time of the Prepared MTB Orodispersible Tablet:

The effect of pH on conventional disintegration time of the prepared MTB orodispersible tablet was done using Erweka disintegration apparatus with 0.1N HCl solution (pH 1.2) and phosphate buffer (pH 6.5) as the disintegration media.

Results and Discussion

Effect of Super Disintegrants Types and Concentrations on the Disintegration Time in the Mouth of the Prepared Control Orodispersible Tablets:

Table (2) shows that the best super disintegrant type was CP with a concentration of 40 mg/tablet. This fact is represented in formula 12, which showed the fastest disintegration time in the mouth (27 sec). Furthermore, to ensure that the super disintegrant critical concentration of CP is 40 mg, another formula (formula 13) was made using 54 mg of CP. It was found that formula 13 disintegrated more slowly than formula 12 and showed mouth disintegration of 29.5 sec. On the other hand, the combination used in formulas 14-16 were not effective in lowering the disintegration time of the orodispersible tablets in the mouth since their disintegration time was relatively high and ranged from 40-60 sec. This may be caused by a competition between these super disintegrants on the little amount of water that found in the mouth knowing that 0.35-1.0 ml/min is the total volume of saliva available under normal conditions [10].

Table (2): The Effect of Super Disintegrants Types and Concentrations on the Disintegration Time in the Mouth of the Prepared Control Orodispersible Tablets *

No	Composition (mg)					Disintegration Time in the mouth (sec)
	SSG	CCS	CP	MCC101	Mg St	
1	4			159	1	44 ± 14
2	8.5			159	1	53 ± 18
3	18			159	1	66 ± 19
4	40			159	1	110 ± 27.3
5		4		159	1	45 ± 13
6		8.5		159	1	45 ± 14
7		18		159	1	42 ± 16
8		40		159	1	79 ± 24
9			4	159	1	58 ± 15.3
10			8.5	159	1	50 ± 20.7
11			18	159	1	39 ± 14.1
12			40	159	1	27 ± 5.1
13			54	159	1	29.5 ± 6.3
14	1.65	1.65	1.65	159	1	43 ± 7.8
15	4.4	4.4	4.4	159	1	40 ± 15
16	9.5	9.5	9.5	159	1	59 ± 18

*Results are expressed as mean ± S.D. (n=3)

Effect of Diluents Types and Concentrations on the Disintegration Time in the Mouth of the Prepared Control Orodispersible Tablets:

The super disintegrant concentration of CP (40 mg/tablet) was kept constant through out this part of the study to find out the best diluent that may be used for the preparation of control orodispersible tablet as shown in (table 3).MCC acts as auxiliary tablet disintegrant because of its water absorbing capacity [11]. The latter advantage gives the reason for the necessity for the inclusion of MCC in the formulation of orodispersible tablets. Practically, no difference was found between MCC 101 (formula 12) and MCC102 (formula 17) and they showed a mouth disintegration of 27 and 28 sec, respectively. Besides, combining two grades of MCC (MCC 101 and MCC 102) as in formula 20 gave slower disintegration time in the mouth (37 sec) than each grade alone.Table (3) also shows that mannitol was better than lactose in preparing

tablet with shorter disintegration time in the mouth. The mouth disintegration time for mannitol containing formula (formula 18) and lactose containing formula (formula 19) were 28 and 37 sec, respectively. This difference in disintegration time may be due to the fact that mannitol has slower dissolution kinetics, that is to say; lactose tends usually to dissolve rather than disintegrate, forming a viscous layer on the surface of the tablet which slows down the penetration of water (or saliva) into the tablet core [(12)]. On the other hand, formula 21 showed slower disintegration time in the mouth (39 sec) than both formulas 18 and 19 indicating that such combination is not effective in lowering the disintegration time in the mouth.Formulas 22-25 were utilized to study the effect of combining MCC 101 and mannitol at different concentrations on disintegration time in the mouth. Although formulas 22, 24 and 25 showed the same disintegration time in the mouth (26 sec), formula 25 was selected to complete the study because it contains the largest amount of mannitol which in turn, imparts sweet and cool taste on the prepared orodispersible tablet.Formulas 26-28 were utilized to study the effect of L-HPC on disintegration time in the mouth of the prepared control orodispersible tablet. It was found that L-HPC prolonged the disintegration time in the mouth at all concentrations, therefore, it can not be used in the preparation of orodispersible tablets.Formulas 29-31 were formulated using three different concentrations of DPD. Formula 30 was disintegrated faster than formulas 29 and 31 indicating that the best concentration of DPD is that used in the preparation of formula 30 (which is 23 mg/tablet and selected later to compete the study).Glycine is used in orodispersible tablet because of its effect as disintegration accelerator. Thus, the addition of glycine decreased the mouth disintegration of the tablet from 25 sec (formula 30) to 23 sec (formula 32). In addition, glycine has good flow and sweet taste, therefore, it was used in the past to hide the bitter taste of saccharine [(13)].Table (3) shows that the best control orodispersible formula (in terms of showing the fastest disintegration time in the mouth) was formula 32 since its disintegration time in the mouth was 23 sec.

Table (3): Effect of Diluents Types and Concentrations on the Disintegration Time in the Mouth of the Prepared Control Orodispersible Tablets (with out MTB) *

Formula	CP	MCC101	MCC102	Mannitol	Lactose	L-HPC	DPD	Glycine	Mg St	Disintegration time in the mouth (sec)
17	40		159						1	28 ± 4.9
18	40			159					1	28 ± 8.5
19	40				159				1	37 ± 12
20	40	80	79						1	37 ± 12.9
21	40	80		69	10				1	39 ± 7.4
22	40	80		79					1	26 ± 4.9
23	40	59		100					1	27 ± 6.4
24	40	40		120					1	26 ± 7.8
25	40	20		140					1	26 ± 7.0
26	40	20		140		2			1	34 ± 10.0
27	40	20		140		23			1	41 ± 9.0
28	40	20		140		50			1	43 ± 8.0
29	40	20		140			11		1	38 ± 7.8
30	40	20		140			23		1	25 ± 9.1
31	40	20		140			50		1	44 ± 11
32	40	20		140			23	55	1	23 ± 5.3

*Results are expressed as mean ± S.D. (n=3)

Formulation of MTB Orodispersible Tablet:

Formula 32 was the best control orodispersible formula, to which MTB, saccharine sodium and flavor were added. Table (4) shows the final MTB orodispersible formula (formula 33) which was subjected to further evaluation tests.

Table (4): Composition of the Selected (Final) MTB Orodispersible Tablet (formula 33).

Material	Amount (mg/tablet)
MTB	10
CP	40
MCC 101	20
Mannitol	140
DPD	23
Glycine	55
Saccharine sodium	2
Flavor	1
Mg St	1
Total weight	292

Physical Parameters Measurement of the Prepared Orodispersible Tablets:

Content Uniformity:

The content uniformity of the prepared MTB orodispersible tablet (formula 33) was complied with BP criteria. No tablet from ten tablets lies out of the range of 85-115% of the label claim. These results indicated that the dosage form had uniform distribution and proper dose of the active ingredient[8].

Hardness:

The hardness of all the prepared orodispersible tablets (with and without MTB) was kept constant at 4 kg by controlling the compression force between approximately 4-7 tone/cm^2.

Friability:

The friability of MTB orodispersible tablet (formula 33) was 0.5% which is acceptable according to BP criteria [8].

Disintegration tests:

Conventional Disintegration Time of the Prepared MTB Orodispersible Tablet (in vitro test):

The conventional disintegration test of the prepared MTB orodispersible tablet (formula 33) as well as Meclodin® and Primperan® tablets (as references) was determined using D.W as disintegration medium. The disintegration time of the prepared MTB orodispersible tablet was only 6 sec. In contrast, the disintegration time of Meclodin® tablet was 220 sec while that of Primperan® tablet was 120 sec as shown in figure (1). The disintegration time of the prepared MTB orodispersible tablet was also shorter than that obtained by other researchers[14].

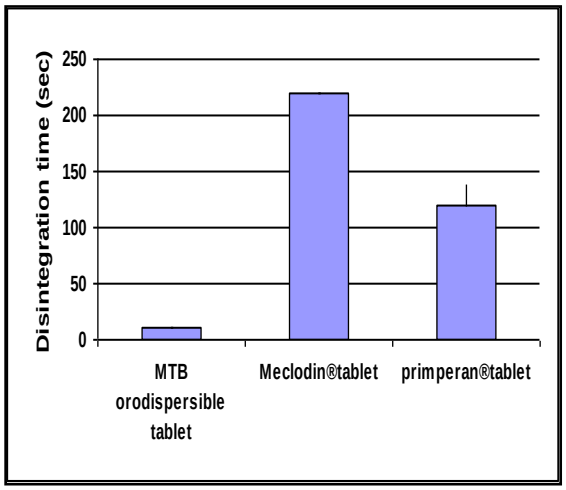

Figure (1): The disintegration time (conventional) of the prepared MTB orodispersible (formula 33), Meclodin® and Primperan® tablets using D.W at 37±0.5 ^{0}C (results are expressed as mean ± SEM, n=3).

Disintegration Time of the Prepared MTB Orodispersible Tablet in the Mouth (in vivo test):

The disintegration time of the prepared MTB orodispersible tablet (formula 33) in the mouth was found to be 23 sec (S.D=7.5, n=15). This result is quite satisfactory regarding BP criteria, which states that the disintegration time of orodispersible tablets in the mouth should not exceed 180 sec [8]. Not only acceptable in terms of BP, formula 33 had faster mouth disintegration than orodispersible tablets prepared by other researchers [15] and also faster than some of the commercialized products. For example, the disintegration time in the mouth of Benadryl® (USA), DuraSolv® (USA), Nimesulide® (Switzerland) and Nippon® (Japan) orodispersible tablets are 40, 45, 30 and 30 sec, respectively [16,17] as shown in figure (2).

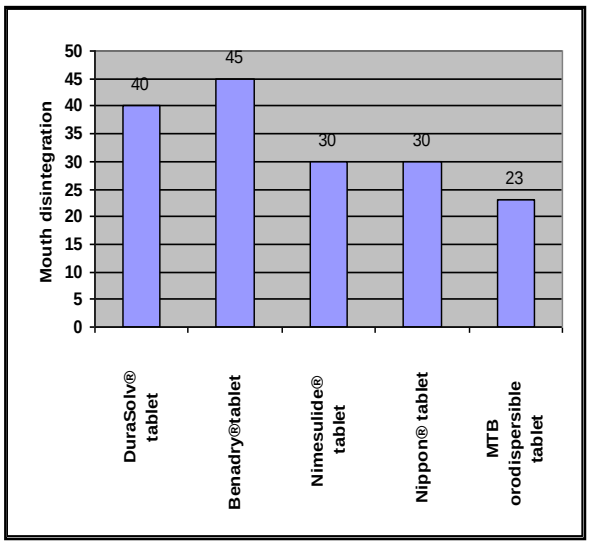

Figure (2): The disintegration time in the mouth of Benadryl®, DuraSolv®, Nimesulide®, Nippon® and the prepared MTB orodispersible tablets (formula 33).

Dissolution Test:

The dissolution test for the prepared MTB orodispersible tablet (formula 33) as well as Meclodin® and Primperan® tablets (as references) was done using 900 ml of D.W as a dissolution medium at 37±0.5 ^{0}C with constant stirring speed of 50 r.p.m for 30 min. Table (5) shows the result of the dissolution test.

Figure (3) indicates that the prepared MTB orodispersible tablet showed faster release rate than both Meclodin® and Primperan® tablets. The release time (T 75%) of the prepared MTB orodispersible tablet was 10-fold and 5-fold faster than that of Meclodin® and Primperan® tablets, respectively.Statistically, there is highly significant difference (P<0.05) among samples at 1, 2, 5, 10 and 15 min time intervals between Meclodin® and the prepared MTB orodispersible tablets. In addition, significant difference was found between samples at 1 and 2 min time intervals between Primperan® and the prepared MTB orodispersible tablets. These facts are clarified in figure (4).To accurately confirm the preference of the prepared MTB orodispersible tablet (formula 33) release profile compared to that of Meclodin® and Primperan® tablets, mathematical expressions had been used. To compare the dissolution profiles of two formulations (test and reference), the difference factor (F_1) and similarity factor (F_2) are useful. The F_1 and F_2 functions can be calculated according to the following equations [18]:

$$F_1 = \left(\frac{\sum_{t=1}^{n} |Rt - Tt|}{\sum_{t=1}^{n} Rt} \right) \times 100$$

$$F_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (Rt - Tt)^2 \right]^{-0.5} \times 100 \right\}$$

indicate clearly the high significant difference among these three formulations.

Table (5): The Percent Release of MTB from the Prepared Orodispersible (formula 33), Meclodin® and Primperan® Tablets in D.W at 37±0.5 ^{0}C *

Time Interval (min)	% Release of MTB from Meclodin® Tablet	% Release of MTB from Primperan® Tablet	% Release of MTB from the prepared MTB Orodispersible Tablet
1	32 ± 2.1 †	42 ± 3.1 †	77 ± 2.3
2	43 ± 2.1 †	55 ± 2.8 †	81 ± 2.3
5	48 ± 0.8 †	84 ± 6.6	88 ± 4.2
10	78 ± 2.1 †	96 ± 3.0	97 ± 1.9
15	95 ± 1.1 †	99 ± 0.5	99 ± 0.2
20	99 ± 0.4	100± 0.0	98 ± 0.8
30	100 ±0.0	99 ± 0.0	99 ± 1.0

* Results are expressed as mean ± S.D (n=3).
† Significant difference (P<0.05)

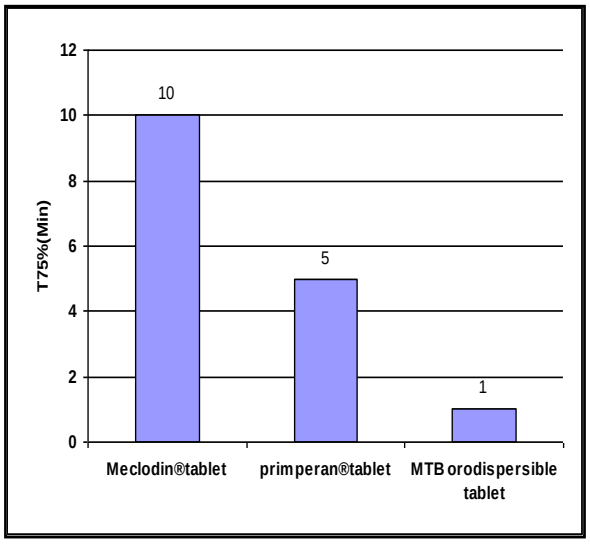

Figure (3): T 75% release of MTB from Meclodin®, Primperan® and MTB orodispersible tablets (formula 33) in D.W at 37±0.5 ^{0}C

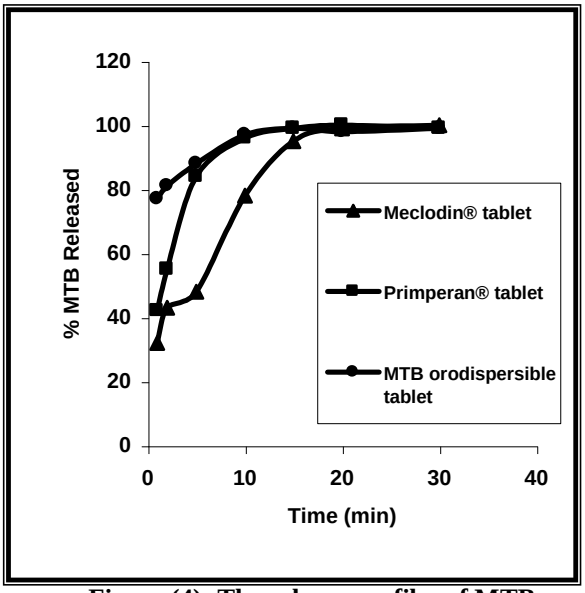

Figure (4): The release profiles of MTB from the prepared MTB orodispersible (formula 33), Meclodin® and Primperan® tablets in D.W at 37± 0.5 ^{0}C.

Effect of pH on Conventional Disintegration Time of the Prepared MTB Orodispersible Tablet:

Two ways are possible to administer orodispersible tablets. The first one is by putting the tablet in the mouth and waiting it to disintegrate without the aid of water. Alternatively, orodispersible tablet can be taken as a conventional tablet by using drinking water to push it down. Hence, two possible pH may face the tablet during its disintegration, which are either the neutral pH (6.5) in the mouth or the acidic pH (1.2) in the stomach [19]. Therefore, conventional disintegration test was made at these two pH so as to reveal the effect of pH, if any, on disintegration time of the prepared MTB orodispersible tablet and to ensure that this tablet disintegrates rapidly in all pHs. The effect of pH on disintegration time of the prepared MTB orodispersible tablet was undergone using Erweka disintegration apparatus with 0.1N HCl (pH 1.2) and phosphate buffer (pH 6.5) as the disintegration media. The disintegration time of the prepared MTB orodispersible tablet was 13 sec in pH 1.2 and 16 sec in pH 6.5 as shown in figure (4).It is obvious from these results that the disintegration time of the prepared MTB orodispersible tablet was not affected by changing the pH of the disintegration medium. This fact may be due that the super disintegrant (CP) used in the formulation of the prepared MTB orodispersible tablet does not affect by such change in the pH, therefore, tablet disintegration did not affect significantly by the shift of the pH [19].

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