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FORMULATION AND EVALUATION OF MECLIZINE HCl ORALLY DISINTEGRATING TABLETS

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تهدف الطرق الحديثة لانطلاق الدواء الى تحقيق مستوى أفضل لارضاء المريض. احدى هذة الطرق هى تحضيرأقراص تذوب بالفم في غضون بضع ثوان بدون الحاجة للماء. وكان الهدف الرئيسي من هذا البحث هو تحضير اقراص سريعة الذوبان فى الفم لعقار المكليزين ذات استساغة مقبولة لمساعدة المرضى من أي فئة عمرية الذين يعانون من صعوبة فى البلع. عقار المكليزين هيدروكلوريد يستخدم فى حالات القيء وعسر الهضم والغثيان.وقد تم دراسة التفاعل بين عقار المكليزين والسواغات المستخدمة باستخدام جهاز المسح الحرارى التفاضلى. وقد تم صياغة الاقراص سريعة الذوبان بواسطة طريقة الكبس المباشر للعقار والسواغات الاخرى. وقد تم دراسة تأثير التركيزات المختلفة من المواد المفتتة فائقة الفاعلية ومعدل ذوبان الاقراص. وكشفت الدراسات باستخدام جهاز المسح الحرارى بانه لا يوجد تفاعل بين العقار والسواغات المستخدمة. وقد تم تقييم صلابة وتفتيت الاقراص وكذالك معدل انطلاق الدواء. اوضحت النتائج ان صلابة الاقراص تتراوح من ٤,٢ إلي ٥,٦ كيلو ودرجة هشوشة أقل من ١%. وكان الاختلاف في وزن الاقراص ومحتواها من العقار مطابق للمواصفات. وقد اظهرت نتائج معدل انطلاق الدواء أن أكثر من ٩٠% من المادة الفعالة تم انطلاقها من الاقراص في غضون ١٠ دقائق. كما أظهرت نتائج دراسة الاستساغة للاقراص قبولا لدى المتطوعين.

Recent advances in novel drug delivery system aims at achieving better patient compliance. One of these advances is the formulation of orally dissolving tablets (ODTs) which dissolve instantaneously, releasing the drug, within a few seconds without the need of water. The main objective of this paper was to prepare and develop ODTs of Meclizine (MZ HCl) with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age for easy administration. Meclizine HCl is an anti-emetic drug used for management of dyspepsia, heartburn, epigastric pain, nausea, and vomiting. The interaction of meclizine and used excipients was studied using differential scanning calorimetry (DSC). The ODTs were prepared by direct compression method. The effect of varying concentrations of different superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time and dissolution rate was studied. The prepared tablets were evaluated for hardness, friability, disintegration time and in-vitro drug release. DSC studies revealed that no interaction between the drug and the used excipients. All tablets had hardness in the range 4.2-5.6 kp and friability less than 1%. Weight variation and drug content of all formulations were within official limit according to BP. In-vitro drug release study of ODTs tablets showed that more than 90% of the drug was released within 10 min. Palatability test by 12 volunteers showed acceptable taste and mouth feel. Thus, results obtained conclusively demonstrated successful rapid disintegration of the formulated tablets and acceptable palatability.

INTRODUCTION

Formulations administered via the oral routes of drug administration represent 50-60% of the total dosage forms. The oral route of administration is considered as the most widely accepted route because of its convenience, ease of administration, pain avoidance and patient

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compliance. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Many pediatric and geriatric patients are unwilling to take solid preparations due to a fear of choking. Also the swallowing of oral dosage forms needs water which is sometimes not available[1]. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[2&3]. These tablets are called fast dissolving tablets, orally disintegrating tablets (ODTs) or mouth-dissolving tablets. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva[4]. Orally disintegrating tablets are considered as solid oral preparations that disintegrate rapidly in the oral cavity with an *in-vitro* disintegration time less than 30 seconds, when based on the United States Pharmacopeia disintegration test method and FDA guidance[5].

The basic approach in development of fast disintegrating tablets (FDT) is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet after putting on the tongue. The bioavailability of some drugs may be increased due to absorption of part of drug in the oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to conventional tablet[6].

Meclizine HCl (MZ HCl) is a first-generation antihistamine of the piperazine class. Meclizine is structurally and pharmacologically similar to buclizine, cyclizine, and hydroxyzine, but has a shorter half-life of 6 hrs compared to cyclizine and hydroxyzine with about 20 hrs. It is used as an antivertigo/antiemetic agent, specifically in the prevention and treatment of nausea, vomiting, and dizziness associated with motion sickness. It possesses anticholinergic, central nervous system depressant, and local anesthetic effects. Its antiemetic and antivertigo effects are not fully understood, but its central anticholinergic properties are partially responsible. The drug depresses labyrinth excitability and vestibular stimulation, and it may affect the medullary chemoreceptor trigger zone[7].

The aim of the present work was to prepare MZ HCl fast dissolving tablets by direct compression method and to study the effect of the type and concentration of different superdisintegrants on the physical properties of the prepared tablets. The direct compression technique was selected rather than wet granulation because the porous nature of the prepared tablets by direct compression gives faster disintegration.

MATERIALS AND METHODS

Meclizine Hydrochoride (MZ HCl) was kindly donated from Chemical Industries Development (CID) Co., Cairo, Egypt. Microcrystalline cellulose (Avicel PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). Spray dried mannitol (Mannogem^{TM} EZ), used as a filler for the orally disintegrating tablets, was kindly supplied by SPI, Grand Haven, USA. Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) and Crospovidone (CPV) were kindely supplied by Riyadh Pharma, Riyadh, KSA. Magnesium stearate was purchased from Riedel-de Haën, Seelze, Germany. Potassium dihydrogen orthophosphate and Sodium hydroxide were purchased from Merck, Darmstadt, Germany.

Methodology

Differential scanning calorimetry (DSC)

The thermal behavior of MZ HCl alone as well as its physical mixtures with tablet excipients was studied using DSC technique. The sample (3-5 mg) was hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25°C to 250°C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N_2 was used as purging gas at rate of 30 ml/min.

Preparation of MZ HCl tablets by direct compression method

The corresponding amounts of MZ, avicel pH 101 and superdisintegrant (Table 1) were accurately weighed and mixed using Turbula mixer (Erweka, S2Y, Heusenstamm, Germany) for five minutes. Thereafter, the corresponding amount of mannitol was accurately weighed, added to the mixture and mixed for 10 min. Finally the amount of magnesium stearate was mixed with the powder in the turbula mixer for further 2 min. The powder was compressed into tablets weighing 200 mg using Korsh single punch machine with 9 mm shallow concave punches (Erweka, EKO, Germany).

Evaluation of the prepared tablets

Weight variation

Twenty tablets from each batch were individually weighed (Analytical balance, Shimadzu, EB-3200D, Tyoto, Japan), the average weight and standard deviation were calculated.

Thickness

Ten pre-weighed tablets were tested for thickness using a micrometer (Starrett, Athol MA, USA), the average thickness and standard deviation were calculated.

Hardness

Tablet hardness was determined with the Hardness Tester (Pharma test GmbH, Hainburg, Germany) for 10 tablets (with known weight and thickness) of each batch; the average hardness and standard deviation were reported.

Friability

Tablet friability was determined according to USP30-NF25. In brief, twenty tablets were weighed (W_1) and placed into the friabilator (Erweka, TA3R, Heusenstamm, Germany), which was rotated at 25 rpm for 4 min. The tablets then reweighed after removal of fines (W_2), and the loss % was calculated by:

$$100 \times (W_1 - W_2)/W_1.$$

MZ HCl content

A meclizine HCl orally disintegrating tablet weighing 200 mg and equivalent to 25 mg meclizine was accurately weighed, finely powdered, and transferred into a volumetric flask. About 60 ml of 0.1 N HCl was added, sonicated for 10 min, then shaken by mechanical means for 30 min and completed to 100 ml with the same solvent and then sonication and filtration was performed. The drug content was determined spectrophotometrically at 232 nm[8]. Test was performed on placebo, fresh, and conditioned meclizine ODT and repeated in triplicates.

***In-vitro* disintegration**

In-vitro disintegration test was assessed according to the USP30-NF25 requirements. One dosage unit was introduced into each of the six tubes of the basket (Electrolab, ED-21, Mumbai, India). The apparatus was operated, using phosphate buffer (pH 6.8) as the immersion fluid, maintained at 37°C ± 2°C. Time for complete disintegration of each tablet was determined and standard deviation of 6 tablets was calculated.

***In-vitro* dissolution studies**

The release measurements were performed using USP dissolution apparatus 2, paddle method, (Caleva Ltd., Model 85T), at 100 rpm using a continuous automated monitoring system. This system consists of an IBM computer PK8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cell spectrophotometer Model PU 8620, Epson FX 850 printer, and Watson-Marlow peristaltic pump using in each flask a 500 mL 0.1N HCl, pH 1.2. The temperature was maintained at 37±0.5°C. At predetermined times intervals (5, 10, 15, 20 and 30 min), absorbances were recorded automatically at 232 nm and the percentage of drug released was determined as a function of time. Test was done on MZ HCl containing tablets in triplicates.

***In-vivo* disintegration and palatability studies**

A taste panel consisting of 12 healthy male volunteers (30-55 years old) have tried a selected formula (F3). The tested tablet was kept in mouth until disintegration, then disgorged. The taste, its extent, after taste and other effects such as numbness if any were evaluated as shown in table 2.

Table 1: Composition of various meclizine HCl oral disintegrating tablet formulations.

Formula	Ingredients (%w/w)						
	MZ	MCC	Mannitol	CCS	SSG	CPV	Mg-Stearate
F1	12.5	43.25	43.25	-	-	-	1
F2	12.5	42.25	42.25	2.0	-	-	1
F3	12.5	40.75	40.75	5.0	-	-	1
F4	12.5	38.25	38.25	10.0	-	-	1
F5	12.5	42.25	42.25	-	2.0	-	1
F6	12.5	40.75	40.75	-	5.0	-	1
F7	12.5	38.25	38.25	-	10.0	-	1
F8	12.5	42.25	42.25	-	-	2.0	1
F9	12.5	40.75	40.75	-	-	5.0	1
F10	12.5	38.25	38.25	-	-	10.0	1

Tablet weight: 200 mg
MZ: Meclozine, MCC: Microcrystalline cellulose (Avicel PH 101), CCS: Crosscarmelose sodium, SSG: Sodium starch glycolate, CPV: Crosspovidone.

Table 2: Palatability evaluation.

Effect	Scale				After Effects
	1	2	3	4	+
Taste	Bad	Acceptable	Good	Excellent	After taste
Mouth feel	Gritty	Acceptable	Good	Excellent	Numbness

RESULTS AND DISCUSSION

DSC study

Figures 1a and b show the DSC thermograms of MZ HCl alone, excipients alone (mannitol, SSG, CPV and CCS) and the physical mixture of MZ HCl and excipent (1:1). It is clear that MZ HCl exhibits an endothermic peak at about 210ºC due to melting of the drug. This endothermic peak has been seen again in the physical mixture of MZ HCl with excipients with lower intensity due to the dilution effect. However, in case of physical mixture of MZ HCl and mannitol, the endothermic peak of MZ HCl disappeared. This might be due to the solubility of MZ HCl in the molten mannitol (m.p. 170ºC). IR study was conducted to detect any chemical interaction of MZ HCl with mannitol, which shown in figure 2. It is clear from this figure that there is no chemical interaction between MZ HCl and mannitol as the characteristic peak of MZ HCl (1392 cm^{-1}) appeared again in the physical mixture with no shift.

Tablet evaluation

The orally disintegrating tablets containing 25 mg MZ HCl was successfully prepared using direct compression method. The manufactured ODTs were evaluated for their weight uniformity, thickness; hardness, friability, MZ HCl content as well as disintegration time, and the obtained data are summarized in table 3. The weight of the tablets in all formulations was found to be in the range of 0.199 g – 0.202 g and the average tablet thickness was found to be 3.5±0.1 mm. Moreover, the tablets exhibited acceptable friability that is less than 1% in all ODTs formulations.

Tablet disintegration

The effect of different disintegrants on the disintegration time of ODTs containing 25 mg MZ HCl is displayed in table 3 and figure 3. It is clearly evident from the data that the used superdisintegrants cause a pronounced decrease in the disintegration time of the prepared ODTs, especially CCS and CPV. Tablets formulated without superdisintegrants exhibited disintegration time of about 36 seconds.

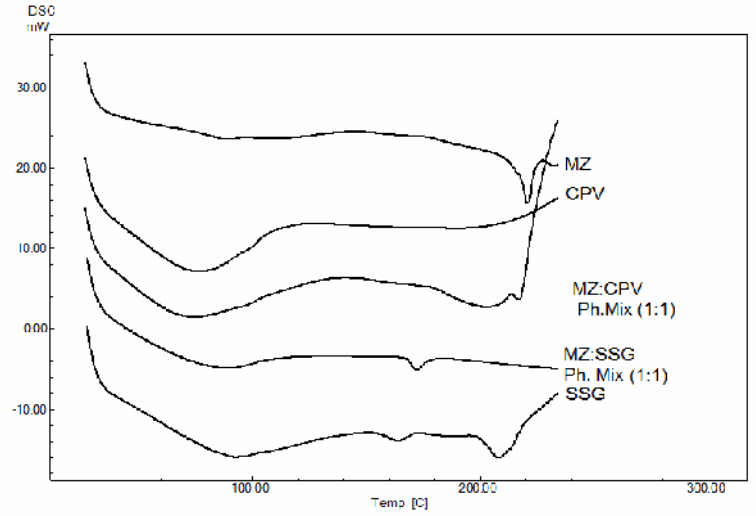

Fig. 1a: DSC thermograms of MZ HCl alone, SSG alone, CPV alone and their physical mixtures (1:1).

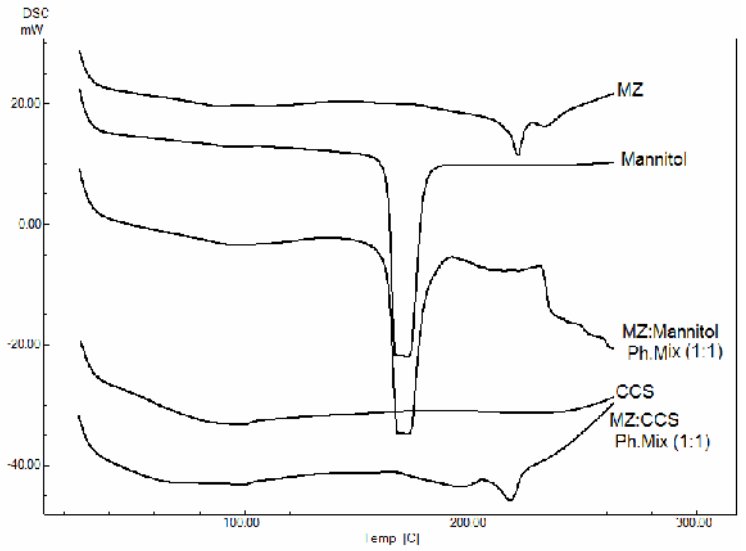

Fig. 1b: DSC thermograms of MZ HCl alone, CCS alone, Mannitol alone and their physical mixtures (1:1).

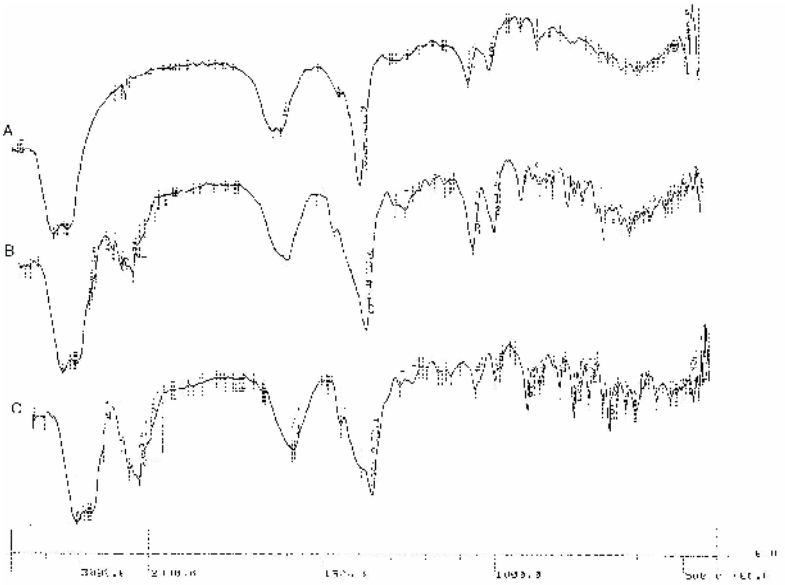

Fig. 2: IR spectra of (A) Mannitol alone, (B) MZ HCl alone, and (C) Mannitol-MZ HCl physical mixtures (1:1).

Table 3: Physical properties of Meclizine HCl orally disintegrating tablets (Mean± SD).

	Weight (g)	Disintegration time* (sec.)	MZ HCl Content (%)	Hardness (Kp)	Friability (%)
F1	0.199 ± 0.39	36 ± 0.58	101.32 ± 0.51	4.50 ± 0.50	0.9960 ± 0.30
F2	0.201 ± 0.54	15 ± 0.87	99.37 ± 0.42	5.21 ± 0.28	0.8210 ± 0.21
F3	0.200 ± 0.72	13 ± 0.58	98.66 ± 0.54	4.80 ± 0.16	0.8710 ± 0.34
F4	0.204 ± 0.63	13 ± 0.10	100.60 ± 0.64	5.80 ± 0.17	0.7430 ± 0.24
F5	0.198 ± 0.61	33 ± 0.58	101.30 ± 0.82	5.50 ± 0.21	0.7980 ± 0.36
F6	0.202 ± 0.37	25 ± 1.00	99.37 ± 0.56	5.80 ± 0.23	0.7013 ± 0.41
F7	0.199 ± 0.49	23 ± 1.00	102.33 ± 0.62	5.60 ± 0.33	0.7510 ± 0.27
F8	0.201 ± 0.73	18 ± 1.53	102.10 ± 0.88	5.60 ± 0.26	0.7610 ± 0.30
F9	0.199 ± 0.68	11 ± 0.58	102.22 ± 0.63	5.20 ± 0.49	0.7730 ± 0.41
F10	0.202 ± 0.38	12 ± 1.00	101.34 ± 0.64	4.21 ± 0.31	0.9530 ± 0.37

* Experiments were carried out in phosphate buffer (pH 6.8).

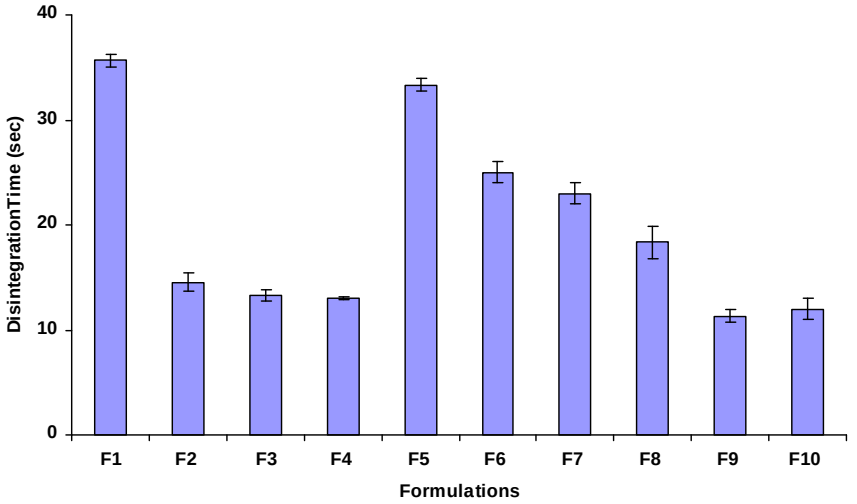

Fig. 3: *In-vitro* disintegration time of all formulations of MZ HCl tablets in phosphate buffer, pH 6.8.

In case of using CCS and CPV as superdisintegrants, increasing the super-disintegrant concentration from 2% to 5% resulted in enhancing tablets disintegration by decreasing disintegration time. In addition, increasing the concentration of CCS and CPV from 5% to 10% in the tablets did not show any significant increase in the disintegration rate. Also, increasing the concentration of SSG from 2% to 5% resulted in a pronounced reduction of disintegration time from 33 seconds to 25 seconds, while increasing the concentration of the superdisintegrant from 5% to 10% did not show any significant action. It can be concluded that the optimum concentration of the superdisintegrant is 5%, which gave rapid disintegration of MZ HCl tablets. These results are in accordance with Shankarrao *et al.*[9], who showed that a concentration of 5% CCS gave minimum disintegration time and the maximum dissolution rate. Also, Ferrero *et al.*[10], studied the disintegration efficiency of croscarmellose sodium and reported that at high concentrations (> 8%), the disintegration time was found to increase. Moreover, Jagdale *et al.*[11], mentioned that croscarmellose sodium gave a low disintegration time initially and then a sudden rise occurs from 4 to 6%. They interpreted these results on the basis of that the disintegration action of croscarmellose sodium at low concentrations in tablet is due to its fibrous nature, which allows wicking of water into tablet matrices. At lower concentrations the fibrous nature is more pronounced and smoothens gradually with time. At high concentrations, there is a probability that wicking and swelling occurs simultaneously

thus, smoothening the particles and the width of the pore decreases.

It could be concluded that tablet formulations containing 5% CCS and 5% CPV (F3 and F9, respectively) could be considered as optimum due to their shortest disintegration time.

In-vitro dissolution

The *in-vitro* dissolution profiles of MZ HCl from the prepared oral disintegrating tablets are displayed in figures 4-6. The drug exhibited only 5% dissolution from the tablet formula containing no superdisintegrant after the first 5 min, and completed dissolution after 15 min. This observation is complying with the higher disintegration time obtained with such formula (36 seconds). However, the presence of superdisintegrants in the tablet formulations caused an enhanced initial dissolution rate of MZ HCl, especially at 5% superdisintegrant level. For example, 95.67, 93.67, 97.33% of the loaded MZ HCl were dissolved from ODTs containing 5% concentration of CCS, CPV and SSG, respectively.

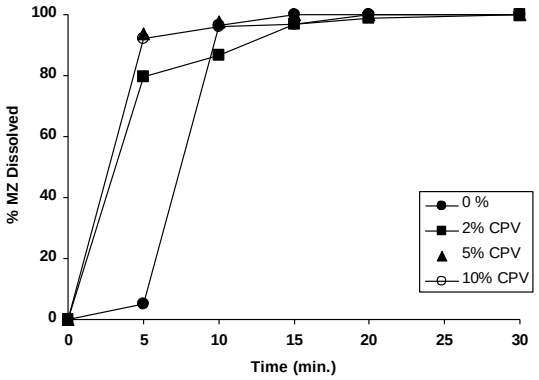

Fig. 4: Effect of concentration of CPV on the % MZ HCl dissolved in 0.1 N HCl, pH 1.2.

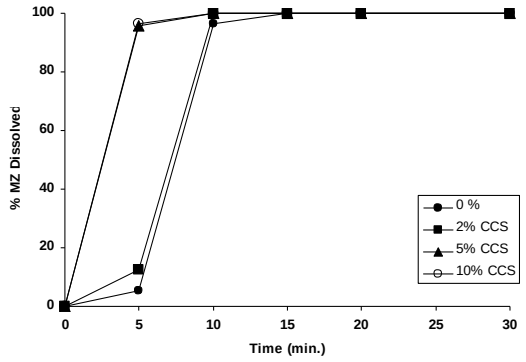

Fig. 5: Effect of concentration of CCS on the % MZ HCl dissolved in 0.1 N HCl, pH 1.2.

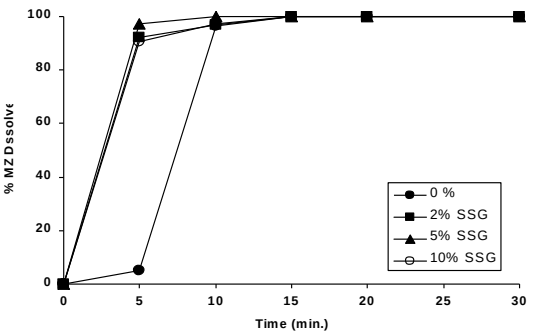

Fig. 6: Effect of concentration of SSG on the % MZ HCl dissolved in 0.1 N HCl, pH 1.2.

The dissolution of MZ HCl from ODTs formulations F3 and F6 (containing 5% of each CCS and SSG, respectively) was studied in different dissolution media, viz., pH 1.2 and pH 6.8 and the results are displayed in figure 7. The drug exhibited very slow dissolution rates from these formulas in the higher pH value (not more than 17% were released after 30 min), while complete drug dissolution from both formulas was observed after 15 min at low pH (pH 1.2). This phenomenon is due to the lower solubility of MZ HCl in the higher pH values[7]. This might be advantageous during the formulation of MZ HCl ODTs, since the manufactured ODTs formulations containing the drug exhibited rapid disintegration in this higher pH values (pH 6.8), which simulates saliva fluid, while the drug dissolves slowly, which may result in masking its undesirable taste.

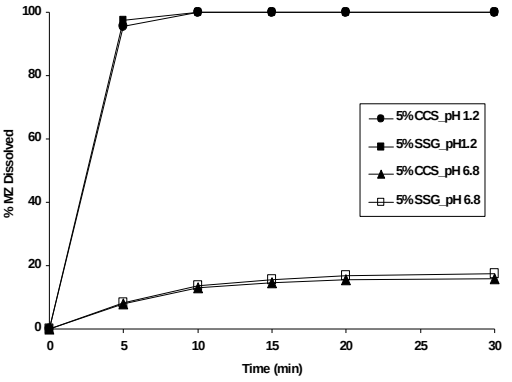

Fig. 7: Effect of pH of the dissolution medium on % MZ HCl dissolved.

Evaluation of palatability

Tables 4&5 show the results of palatability test. Taste evaluation results show that the response of half of the volunteers was acceptable while the other half showed good response. Only two volunteers out of twelve

complained a mild bitter after taste. Mouth feel results show that the response of ten of the volunteers was acceptable while the other two showed good response with no complain of numbness. These results indicate an acceptable palatability of the formulated tablets. The mean *in-vivo* disintegration time for the 12 volunteers was about 10 seconds which is in accordance with the *in-vitro* disintegration time for F3.

Table 4: Taste evaluation results for the selected formula (F3).

Volunteer No.	Scale				After taste	*In-vivo* disintegration time (sec.)
	1	2	3	4	-	
1			X		-	8
2			X		+	8
3		X			+	13
4			X		-	5
5			X		-	10
6			X		-	10
7			X		-	15
8		X			-	12
9		X			-	8
10		X			-	8
11		X			-	8
12		X			-	10

Table 5: Mouth feel evaluation results for the selected formula (F3).

Volunteer No.	Scale				Numbness
	1	2	3	4	
1		X			-
2			X		-
3		X			-
4			X		-
5		X			-
6		X			-
7		X			-
8		X			-
9		X			-
10		X			-
11		X			-
12		X			

On conclusion, ODTs of MZ HCl were developed with sufficient mechanical integrity, content uniformity with acceptable palatability to assist patients of any age group for easy administration. The ODTs were prepared by direct compression method. All tablets had hardness in the range 4.2-5.6 kp and friability less than 1%. Weight variation and drug content of all formulations were within official limit. *In-vitro* drug release study of ODTs tablets showed that more than 90% of the drug was released within 10 min.

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