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STABILITY STUDY OF FAMOTIDINE EFFERVESCENT TABLETS PREPARED BY A SEPARATED GRANULATION TECHNIQUE

A. M. Aly and M. K. Qato

Faculty of Pharmacy, Alisra University, Amman, Jordan

عقار الفاموتيدين المضاد لمستقبلات الهيدروجين والمستخدم كثيرا لعلاج أمراض قرحة المعدة. لقد تم تحضير أقراص الفاموتيدين الفوارة بطعم مقبول وصفات طبيعية جيدة وأيضا سريعة التفتت فى الماء وذلك بتحضير حبيبات بإستخدام النعناع والتوتى فروتى والكراميل كمكسبات للطعم. ومن أجل تحضير أقراص فوارة لها درجة ثبات أفضل عند تخزينها بإستخدام التوتى فروتى (حيث أفضل طعم تم تحضيره) تم تحضير أقراص فوارة بإستخدام طريقة مبتكرة لتحضير الحبيبات. وذلك بتحضير نوعية من الحبيبات أحدها تحتوى على المكونات الحامضية والفاموتيدين والأخرى على المكونات القاعدية. وقد تم دراسة ثبات الأقراص المحضرة بالطريقتين فى درجة حرارة الغرفة (٢٥°م) وذلك بإحتواء الأقراص داخل ثلاث طرق مختلفة للتغليف وهى: الأولى داخل علبة بلاستيكية والثانية بلفها فى رقائق الألومنيوم والثالثة بإستخدام علبة بلاستيكية وبداخلها مادة ماصة للرطوبة. وكان معيار درجة الثبات للأقراص هو نقص زمن تفتتها. وقد أشارت دراسة الثباتية بأن الأقراص المحضرة بطريقة التحبب المنفصل لها درجة ثبات عالية بدون فروق واضحة للطرق المختلفة للتعبئة ، بينما الأقراص المحضرة بطريقة التحبب الغير منفصل كانت أكثر ثباتا عند تعبئتها فى زجاجة بلاستيكية ملفوفة فى رقائق الألومنيوم ومحتوية على المادة الماصة للرطوبة. ومن هذه الدراسة يمكننا أن نستخلص أن تحضير الأقراص الفوارة بطريقة التحبب المنفصل هى الأفض ولا تستوجب تغليفا خاصا.

Famotidine is a highly selective H_2-receptor antagonist widely used in the treatment and prevention of peptic ulcer disease. Famotidine effervescent tablets (ET) with acceptable taste and physical properties and rapid disintegration time were prepared by wet granulation using peppermint, tutti frutti or caramel as flavoring agents. Aiming for the production of more stable ET; the formula containing tutti frutti, which has the most acceptable taste, was chosen to prepare ET utilizing a modified wet granulation technique. This involve the production of two separated granulations; one containing the acidic ingredients with the drug, and the other containing the basic ones. The stability of the two prepared formulations, at room temperature (25°), were also studied by storing each formula inside three different packaging systems. The first inside a plastic bottle alone, the second were wrapped in aluminum foil while in the third one, the bottle included a desiccant. The decrease in the disintegration time values upon aging was detected as a parameter for the ET stability. The stability study revealed that; tablets prepared by separated granulation showed a pronounced enhancement of stability without significant difference between each of the three packaging systems. Whereas, tablets stored in plastic bottles after wrapping in aluminum foil including a desiccant showed the best stability results for total granulation technique. This indicates fewer requirements of special packaging for tablets prepared by the promising separated granulation method.

INTRODUCTION

Effervescent tablets (ET) are popular dosage forms due to the pleasant taste of carbonated solutions and to the psychological effect. Improvement of bioavailability of many drugs by effervescent tableting has been investigated.[1-8] Practically, effervescent tablets can be prepared by one of the following technique; 1) direct compression technique

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utilizing one of the water soluble direct compressible vehicles, 2) dry granulation; using a roller compactor, Chilsonator, or pre-tableting technique, or 3) by wet granulation. This technique utilizes one of three different methods: a) the use of heat involving the release of water from hydrated ingredient (e.g. hydrous citric acid), b) the use of non-reactive liquid (e.g. ethanol or ethyl acetate), or c) the use of reactive liquid, usually water, through which care must be taken to maintain the finished product effervescent character,[9] or 4) the preparation of two-layer effervescent tablets. This last technique requires a special tableting equipment, but it is more difficult since adequate binding and lubricating are needed for each layer.[10] Many water-soluble excipients; e.g. diluents and lubricants have been evaluated for the production of efficient and stable ET.[11,12]

Famotidine is a highly selective H_2-receptors antagonist without agonist or antagonist effects on histaminergic H_1-muscarinic, nicotinic, and adrenergic receptors.[13]

The aim of this investigation is to prepare famotidine effervescent tablets with acceptable taste using different flavouring agents. Also, to prepare a formula of famotidine ET of the most acceptable taste by separated granulation technique and to study their stability when included inside three different packaging systems.

EXPERIMENTAL

Materials

Famotidine powder (Gedeon Richter LTD, Hungary). Aspartame, Direct compressing sugar, caramel and tutti frutti oil (Dar Al-Dawa Company, Jordan). Citric acid (Gainland Chemical company, U.K.). Tartaric acid (Lonover House, England). Sodium bicarbonate (Chemlab Co., England). Polyvinyl pyrrolidone (ISP Technologies. INK, U.K.). Polyethylene glycol (PEG 6000) (Janssen Chemica, Belgium).

Preparation of the granules

Indrayanto *et al.*,[12] stated that famotidine was incompatible with many excipients, e.g. lactose, dihydrogen calcium phosphate (Emcompress), kolidon and Primojel. The modified sodium bicarbonate was obtained by heating sodium bicarbonate, at 100° for 45 min in an oven, in order to convert the surface of its particles to sodium carbonate. This conversion (5-10%) gives a better compression characteristics with less hygroscopic properties than the common carbonate.[14-27] Also, famotidine was dried at 70° for one hour. The following constituents (in mg) were suggested for preparing 300 mg famotidine ET:

Famotidine	20
Aspartame	18
Citric acid	25
Tartaric acid	50
Sodium bicarbonate	76
Polyethylene glycol (PEG 6000)	12
Polyvinyl pyrrolidon (PVP)	3
Direct Compression Sugar	94.5
Flavouring agent	1.5

Preparation of total granulation

The specified amount of Famotidine, Aspartame, Citric acid, Tartaric acid, and Sodium bicarbonate were passed through a sieve of 500 μm mesh screen and then thoroughly mixed for 10 min in a cube mixer (Erweka, Germany). Polyvinyl pyrrolidone (PVP) in 20% w/v, was dissolved in a small amount of ethanol with either peppermint oil (F1), tutti-frutti oil (F2), or caramel powder (F3). This binding solution was then added dropwise to the prepared mixture to form a paste with suitable consistency to pass through 500 μm mesh screen. The produced granules were then dried using fluid bed drier (Sherwood Scientific Cambridge, England) at 35° for 15 min with air velocity of 370 ft/min . The dry granules were milled in a mortar, and passed through 355-μm-mesh screen.

Preparation of separated granulation

The same procedures were applied except that PVP solution was divided into two portions; the first for preparing the acid granules (containing citric and tartaric acids and

aspartame) while the second for the basic ones (including sodium bicarbonate and famotidine). The two granulations, after sieving, were then thoroughly mixed (F4).

Preparation of effervescent tablets

Each type of the prepared granules were then mixed with the specified amount of Polyethylene glycol 6000 and direct compression sugar in the cube mixer; and then compressed into 0.3 g tablets (8 mm diameter) with flat faced punches using a Korsch (EK10, Germany), constant rate, tabletting machine. The machine was adjusted to obtain tablets of hardness between 80-90 Newton in every case.

Evaluation of tablets

Uniformity of weight and diameter, as well as the friability (loss %) of each formulation were determined according to the USP/NF (1995) procedure and specifications. The hardness of tablets was determined using Erweka hardness tester and the thickness was also determined. The tensile strength (Ts) was calculated from the equation; $Ts = 2H / \pi TD$, where H is the hardness, T is the thickness and D is the diameter of tablets. The standard deviation and coefficient of variation percent, C.V.%, were calculated.

Famotidine content for each batch was determined by extraction with phosphate buffer (pH 7.4) until complete dissolving of the drug then filtration. The concentration of drug in the filtrate was detected spectrophotometrically at 265 nm according to USP/NF (1995) test for the uniformity of drug content.

Evaluation of tablet taste (palatability test)

A statistical study was made to evaluate the taste of each of the prepared formulae. A random sample of 100 students examined the taste of the solution of the effervescent tablets from each formula to test their palatability.

Stability Study (depending on the disintegration time)

The time required for complete disintegration and solubilization of 6 tablets in a beaker containing 100 ml of tap water at 25° was determined, and the average and C.V.% were calculated for each batch. Also, the stability of the prepared tablets could be detected by determining the disintegration (dissolution) time for each batch after storing the tablets at ambient temperature and humidity (shelf life). The decrease in the disintegration time values upon aging was detected as a parameter for the ET stability.[9] Three types of packaging systems were utilized for studying the stability: a) Plastic bottle only, b) Plastic bottle after wrapping the tablets with aluminum foil, and c) Plastic bottle in aluminum foil including calcium chloride (0.5 g) as a desiccant.

RESULTS AND DISCUSSION

Famotidine, which is an H_2 blocker, has anti-ulcer activity. It has a bitter taste. In this work many trials have been tested to produce famotidine acceptable tablets, using aspartame as a natural and safe sweetening agent without a bitter after taste. Three tablet formulations could be produced by adding three different flavoring agents namely; peppermint oil (F1), tutti-frutti oil (F2), or caramel powder (F3). The prepared tablets showed acceptable hardness values (i.e. suitable for effervescent tablets). The friability values fulfilled the USP/NF (1995) requirements. Also, the formulation's uniformity of weight and diameter were acceptable according to the USP/NF (1995). The thickness values were, also, suitable (Table 1). The drug content test results, Table 1, showed that all the prepared formulations fulfilled the USP/NF (1995) requirements. Upon studying the disintegration time of each of the prepared formulae, rapid rate of dissolution (less than two min), and clear solutions without any turbidity were observed after effervescence of each tablet formulation.

From the results of palatability test, in Fig. 1, it could be possible to detect that the most acceptable formula was "F2", followed by F1, while F3 formula was the less acceptable one. Thus, F2 was chosen for preparing famotidine ET by a separated granulation technique. Upon studying the stability of the prepared tablets depending on the disintegration time,[9] it could be possible to observe that: generally the disintegration time of all the prepared tablets

Table 1: Physical properties of the prepared famotidine tablets.

Parameter / Symbol	Uniformity of drug content (mg)	Uniformity of weight (g)	Uniformity of diameter (mm)	Uniformity of thickness (mm)	Tensile strength (N/cm^2)	Friability value (Loss %)	Disintegration time (seconds)
F1	19.30 (2.891)*	0.3027 (0.890)	8.095 (1.917)	4.956 (0.063)	88.54 (1.602)	0.671	48 (1.15)
F2	21.01 (1.690)	0.3095 (1.744)	8.027 (1.640)	4.975 (0.990)	92.12 (1.540)	0.732	85 (0.648)
F3	17.80 (3.095)	0.3020 (1.068)	8.080 (0.987)	4.942 (1.277)	88.66 (1.118)	0.865	57 (1.55)
F4 (Sep. Gr.)	18.69 (4.652)	0.3033 (1.521)	8.011 (0.071)	4.857 (0.192)	95.22 (3.524)	1.025	118 (0.886)

* Values between parentheses are the coefficient of variation (C.V.%).

increased by time but to different extents (Table 2 and Figs. 2-4). Tablets prepared by separated granulation showed pronounced enhancement of stability indicated by minor effects on disintegration time during storage compared to the other formulations prepared by total granulation specially those which were packaged solely inside plastic bottles. Tablets stored in plastic bottles after wrapping in aluminum foil including desiccant showed the best stability results for total granulation technique. No marked difference could be detected due to the presence or absence of aluminum foil or desiccant for the formulations prepared by the suggested separated granulation method. This result indicates that the separated granulation technique produced effervescent tablets of comparatively better stability. The comparatively better stability of the separated granulation technique may be explained by the lower contact between the highly reactive acids and bases by preparing each in separated granules. This apparently resulted in retardation of the expected reaction during storage, with a subsequent better stability.

Conclusion

From the previous results, it could be concluded that; all the prepared Famotidine ET formulations have acceptable physical properties. The drug content values fulfil the USP/NF (1995) requirements. Also, the disintegration time results were excellent for the effervescent tablets. The formula containing tutti frutti showed the most acceptable taste followed by those including peppermint oil formula, while those containing caramel revealed least acceptability.

Tablets prepared by separated granulation showed pronounced improvement of stability especially for those packaged solely inside plastic bottles. Tablets stored in plastic bottles after wrapping in Aluminum foil including a desiccant showed the best stability results for total granulation technique. Whereas, no significant difference between each of the three packaging systems was detected in case of the separated granulation method.

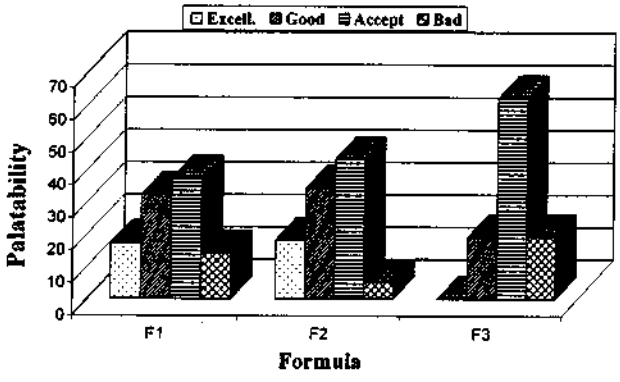

Fig. 1: The palatability statistical test for the prepared famotidine effervescent tablets (ET) using pepperment F1, tutti frutti F2, or caramel F3.

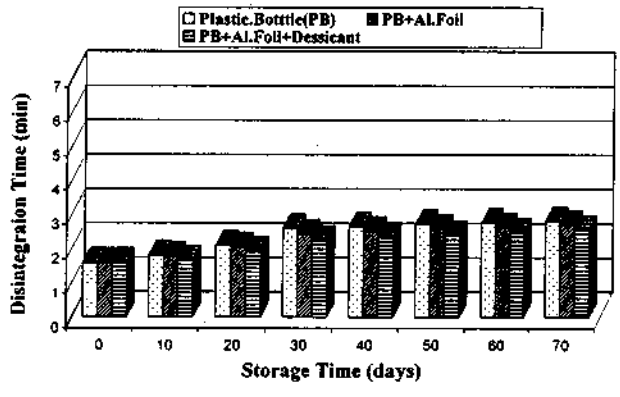

Fig. 2: Effect of packaging system on the stability of famotidine ET prepared by separated granulation technique.

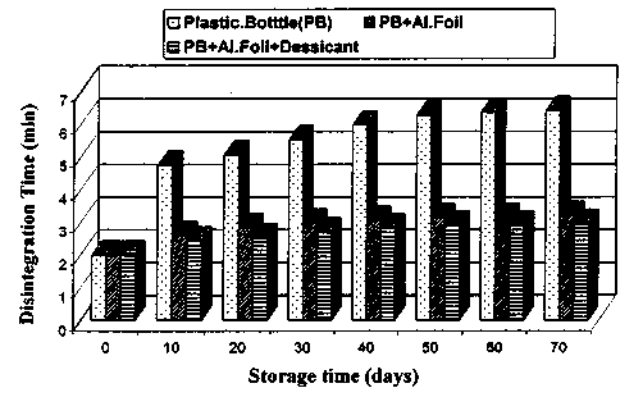

Fig. 3: Effect of packaging system on the stability of famotidine ET prepared by total granulation technique.

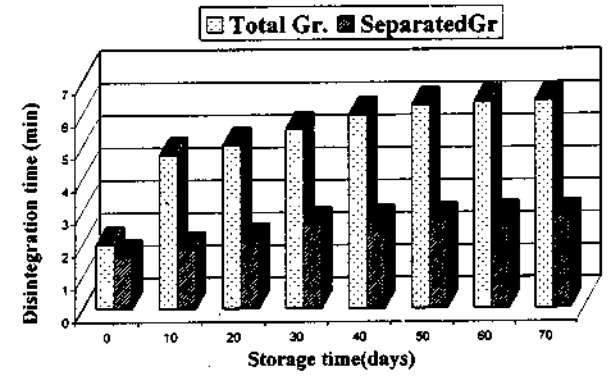

Fig. 4: Effect of plastic bottle packaging on the disintegration time of the prepared famotidine ET.

Table 2: Stability of famotidine effervescent tablets prepared by total or separated granulation (according to disintegration time).

Formula / Time (days)	Disintegration time (min)					
	Plastic bottle		Plastic bottle & Al. foil		Plastic bottle & Al. foil & desiccant	
	Total Gr.	Sep. Gr.	Total Gr.	Sep. Gr.	Total Gr.	Sep. Gr.
0	1.97 (0.886)*	1.58 (0.648)	1.97 (0.886)	1.58 (0.648)	1.97 (0.886)	1.58 (0.648)
10	4.72 (0.519)	1.80 (0.547)	2.57 (1.111)	1.75 (0.617)	2.40 (1.161)	1.65 (2.014)
20	5.03 (0.279)	2.08 (1.707)	2.82 (1.147)	2.03 (1.564)	2.50 (1.304)	1.90 (1.688)
30	5.50 (0.641)	2.57 (0.382)	2.95 (0.545)	2.42 (0.888)	2.67 (1.417)	2.23 (0.654)
40	5.95 (0.359)	2.63 (0.588)	3.03 (0.464)	2.50 (0.609)	2.80 (1.141)	2.32 (0.659)
50	6.25 (0.553)	2.70 (0.950)	3.10 (0.924)	2.57 (1.289)	2.87 (0.905)	2.38 (0.628)
60	6.33 (0.476)	2.75 (1.058)	3.13 (0.905)	2.62 (0.659)	2.88 (0.888)	2.47 (0.649)
70	6.38 (1.069)	2.80 (1.155)	3.18 (0.885)	2.68 (0.928)	2.93 (0.895)	2.55 (1.025)

* Values between parentheses are the coefficient of variation (C.V.%).

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