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IMPLEMENTATION AND COMPARISON OF DIFFERENT TASTE MASKING TECHNIQUES TO DESIGN AND ASSESS DISPERSIBLE TABLET FORMULATIONS

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ABSTRACT
The objective of this study was to assess the efficacy of several taste-masking techniques and to study the impact of different formulation variables on the physicochemical properties of dispersible tablets containing Ranitidine as a model drug. Ranitidine powder was taste masked using various techniques. Factorial design (2^4) was applied to design the set of tablet formulations. The four factors implemented were the manufacturing method, filler type, superdisintegrant type and superdisintegrant concentration. Levels selected were direct compression and wet granulation for the manufacturing method, microcrystalline cellulose and mannitol for the diluent type, sodium starch glycolate and croscarmellose sodium for superdisintegrant type, and 2% and 10% for superdisintegrant concentration. Granulation with calcium carbonate (ratio of 1:8) was the taste-masking method of choice to be implemented. The formulated tablets results revealed that the manufacturing method has a significant influence on all the tested physicochemical properties (p-values < 0.05) such as tablet's weight variation, hardness, friability, and disintegration time. Croscarmellose sodium obtained better results than sodium starch glycolate. Both fillers obtained good properties when implementing direct compression method with croscarmellose sodium concentration of 2%, or wet granulation method with croscarmellose sodium concentration of 10%. Drug release was also increased by increasing concentration of croscarmellose sodium. These findings represent an easy manufacturing procedure with relatively low-cost materials that can be implemented to formulate dispersible tablets of bitter tasting drugs that will enhance patient compliance and lead to faster onset of action.

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INTRODUCTION

In medical therapy, the oral route is the most frequently used route for drug administration. Oral dosage forms are usually intended for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract. Compared with other routes, it has the most compliance, convenience, and safety for patients [1].

Tablets are the most used dosage form because they are convenient, cheap, and easy to make. The ease of administration is the reason behind their outstanding patient compliance. Compressed tablets are commercially manufactured by three general methods. These methods are wet granulation, dry granulation, and direct compression. The method of preparation and the added ingredients are selected to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets [2].

However, the elderly and some children suffer from swallowing difficulties, so conventional tablets may not be suitable for them. To overcome this problem, dispersible tablets were developed. These tablets can be uncoated or film-coated and contain a unique formulation that disintegrates quickly in water to form a homogeneous drinkable suspension [3].

There are two types of dispersible tablets: one type that disintegrates immediately in the mouth without the need for water, and the other one can be dispersed in water to form a dispersion that is easy to be taken by the patient [4], and the latter is the one used in this experiment.

Dispersible tablets offer the following advantages over conventional tablets: they allow high drug loading, offer a pleasant mouth feeling, taste masking is feasible, and leave minimal residue in the mouth following oral intake [4].

Ranitidine -the model drug used in this study- is a Histamine (H2) receptor antagonist that reduces gastric acid secretion. It was commonly used in gastric and active duodenal ulcers, Zollinger-Ellison Syndrome, erosive esophagitis, and gastroesophageal reflux disease (GERD) [5]. And before its withdrawal from the market -in 2020- after an ongoing investigation uncovered levels of a potential cancer-causing substance known as N-Nitrosodimethylamine (NDMA) in the drug [6], the number of Ranitidine prescriptions in 2019 was slightly above 13.5 million prescriptions [7], and with that high number of prescriptions there was a need to consider patients with swallowing difficulties. Also, it is worth mentioning that this study was conducted and completed before the withdrawal of Ranitidine from the market. Therefore, this study aimed to develop a dispersible tablet by assessing the efficacy of several taste-masking techniques and the impact of different formulation variables on the physicochemical properties using Ranitidine as a model drug. To achieve this, Ranitidine hydrochloride powder was subjected to different techniques of taste masking such as solid dispersion, granulation, inclusion complex formation, and combined granulation and inclusion complex formation technique. Then different formulations were prepared, and the effects of selected formulation variables were studied.

MATERIALS AND METHODS

Materials

Mannitol (Pearlitol®), croscarmellose sodium (Solutab®), and sodium starch glycolate (Explotab®) were all products of Roquette, Germany. Microcrystalline cellulose 102 (Vivapur® 102, JRS Pharma, Germany), povidone K30 (Shanghain Yukin, China), ethanol 96% v/v (Scharlau, Spain), magnesium stearate (Peter Greven, Netherlands), and methacrylic acid copolymer (Eudragit® E-100, Evonik, Germany) were all pharmaceutical grade and purchased from commercial sources. Ranitidine HCl was kindly donated by GMC Pharmaceuticals, Sudan. Sucralose, calcium carbonate (compressible grade), and beta-cyclodextrin were all kindly donated by Azal Pharma, Sudan. Other materials and reagents were analytical grades obtained from different commercial sources.

Ranitidine taste masking:

Four different techniques were used for Ranitidine HCl raw material taste-masking distributed over 14 trials (T1-T14) as shown in Table 1.

i) **Solid dispersion**

Ranitidine HCl powder was weighed and mixed with Eudragit E-100 using mortar and pestle in different ratios (T1-T4 in Table 1), the mixture was then transferred into stainless-steel vessels. Then 8 ml of 96% ethanol was added to each 1 g of Eudragit E-100 in the mixture. The new mixture was stirred on a magnetic stirrer using 200 rpm speed at 40°C until a thick gel was formed. The gel was left overnight in a 40°C drying oven to allow the evaporation of ethanol, then the solidified gel was crushed and passed through a 0.5 mm sieve.

ii) **Granulation**

Ranitidine HCl powder was weighed and mixed with calcium carbonate powder in different ratios (T5-T9 in Table 1). Povidone K30 (0.5g for each 1g of Ranitidine HCl) was dissolved in 96% ethanol (1ml for each 1g of calcium

carbonate), then stirred at 350 rpm until the solution became clear. The mixture of Ranitidine HCl and calcium carbonate was granulated using povidone K30 solution until coarse granules were formed, granules were left to dry at 45°C for 4 hours then passed through a 0.5 mm sieve.

iii) **Inclusion complex formation**

Ranitidine HCl with beta-cyclodextrin (β-CD) inclusion complex was formed using two different methods; the kneading method in a molar ratio of 1:1 (T10) and 1:2 (T11), in which β-CD was triturated with purified water using mortar and pestle until a slurry paste was formed. Ranitidine HCl was added to the paste and triturated gently for 15 mins, then the mixture was allowed to dry at 40°C overnight and then passed through a 0.5 mm sieve. The other method is the granulation method using different solvents (water-T12 and 96% ethanol-T13) in which Ranitidine HCl was mixed with β-CD in a 1:3 molar ratio. Granules formed by adding water or 96% ethanol were left to dry at 45°C for 4 hours, then the dry granules were passed through a 0.5 mm sieve.

iv) **Combined granulation and inclusion complex formation**

Ranitidine HCl powder was mixed with calcium carbonate in a 1:4 ratio, then povidone K30 binding solution was prepared by dissolving 0.5 g of povidone for each 1 g of Ranitidine HCl in 96% ethanol (1 ml for each 1 g of calcium carbonate), then this binding solution was used to granulate the Ranitidine HCl and calcium carbonate mixture, granules were left to dry for 4 hours at 45°C, then passed through 0.5 mm sieve. β-CD was weighed and triturated with purified water (1 ml for each 2.5 g of β-CD) until the slurry paste was formed. The dry granules of Ranitidine HCl and calcium carbonate were added to the paste and triturated for 15 mins. The mixture was dried at 40°C overnight, then passed through a 0.5 mm sieve.

Evaluation of taste masking trials:

Informed consent was obtained for this experiment and the privacy rights of the volunteers are maintained.

Taste masking for trial formulations was evaluated using a taste panel of six healthy human volunteers (three adult males "V1-V3" and three adult females "V4-V6"). In this test, volunteers were given a very small sample of the pure drug Ranitidine HCl, and equivalent samples from trial formulations to taste and assess the bitterness by responding after ten seconds. A response scale was developed, in which taste is given a value from 1 to 5 depending on bitterness, where 1= not bitter/ fully taste-masked, 2= very slightly bitter, 3= slightly bitter/acceptable, 4= bitter, and 5= extremely bitter.

Experimental design and preparation of dispersible tablet formulations:

From the taste masking trials, the trial with the most suitable responses was chosen and included in the experimental design. Two levels- four factors (2^4) factorial design was employed in this study with the aid of Design Expert® (V8.0.6) software. Factors studied were manufacturing method, filler type, superdisintegrant type, and superdisintegrant level (% W/W). Levels selected for the manufacturing method were direct compression (DC) and wet granulation (WG), whereas microcrystalline cellulose (MCC) and mannitol were the levels selected for filler type. Croscarmellose sodium (CCS) and sodium starch glycolate (SSG) were selected as the levels for superdisintegrant type and 2% and 10% were the levels for superdisintegrant level. Table 2 shows the layout of the experimental runs for the 2^4 full factorial design.

For each experimental run, taste-masked Ranitidine HCl powder was mixed with superdisintegrant, sucralose (3% w/w), magnesium stearate (0.25% w/w), and the diluent (q.s. to total tablet weight of 1000 mg). For runs prepared by direct compression (F1, F2, F4, F5, F7, F8, F12, and F15), taste-masked Ranitidine HCl was mixed with the diluent, superdisintegrant, and sucralose for 5 mins, then the mixture was passed through 0.5 mm sieve. Magnesium stearate was then added to the mixture and mixed gently for 2 mins. The Mixture was compressed in a tablet press machine using a round bi-concave 13mm diameter punch with the same speed and force for all the formulations. For runs prepared by wet granulation (F3, F6, F10, F11, F13, F14, and F16), taste-masked Ranitidine HCl was mixed with diluent, superdisintegrant, and sucralose for 5 min, the mixture was then transferred to a stainless-steel vessel and granulated using ethanol 96% until coarse granules were formed. The granules were then passed through a 1 mm sieve and allowed to dry at 40°C for 4 hours. The dried granules were passed through a 0.5 mm sieve, and magnesium stearate was added to the mixture and mixed gently for 2 mins. The mixture was then compressed using a tablet press machine equipped with a round bi-concave 13 mm diameter punch.

Table 1: Ranitidine HCl Raw Material Taste Masking Trials

Trial	Taste masking method	Ratio
T1	Solid dispersion	R. HCl : Eudragit E100 (1:1)
T2	Solid dispersion	R. HCl : Eudragit E100 (1:2)
T3	Solid dispersion	R. HCl : Eudragit E100 (1:3)
T4	Solid dispersion	R. HCl : Eudragit E100 (1:4)
T5	Granulation	R. HCl : Calcium carbonate (1:2)
T6	Granulation	R. HCl : Calcium carbonate (1:4)
T7	Granulation	R. HCl : Calcium carbonate (1:6)
T8	Granulation	R. HCl : Calcium carbonate (1:8)
T9	Granulation	R. HCl : Calcium carbonate (1:10)
T10	Inclusion complex formation (Kneading method)	R. HCl : β-CD (1:1) "molar ratio"
T11	Inclusion complex formation (Kneading method)	R. HCl : β-CD (1:2) "molar ratio"
T12	Inclusion complex formation (Granulation with water)	R. HCl : β-CD (1:3) "molar ratio"
T13	Inclusion complex formation (Granulation with ethanol)	R. HCl : β-CD (1:3) "molar ratio"
T14	Combined granulation and inclusion complex formation	R. HCl : Calcium carbonate (1:4), then. R. HCl : β-CD (1:2) "molar ratio"

Table 2: Experimental runs layout for the 2^4 full factorial design

Formulation	Manufacturing Method[1]	Diluent Type[2]	Superdisintegrant Type[3]	Superdisintegrant Level (% W/W)
F1	DC	Mannitol	CCS	10
F2	DC	Mannitol	CCS	2
F3	WG	Mannitol	SSG	10
F4	DC	MCC	SSG	10
F5	DC	MCC	CCS	10
F6	WG	Mannitol	CCS	2
F7	DC	MCC	SSG	2
F8	DC	Mannitol	SSG	2
F9	WG	MCC	SSG	10
F10	WG	MCC	SSG	2
F11	WG	Mannitol	CCS	10
F12	DC	MCC	CCS	2
F13	WG	Mannitol	SSG	2
F14	WG	MCC	CCS	10
F15	DC	Mannitol	SSG	10
F16	WG	MCC	CCS	2

[*] *DC and WG stand for direct compression and wet granulation, respectively.*

[2] *MCC stands for microcrystalline cellulose and*

[3] *CSS and SSG stand for croscarmellose sodium and sodium starch glycolate, respectively.*

Qualification and data analysis of compressed tablets:

Randomly selected samples from all formulations were subjected to pharmacopeial tests according to the United States Pharmacopoeia (USP39-NF34, 2016) and International Pharmacopoeia (for disintegration test) to evaluate the physicochemical properties of the formulations. Results were shown as a mean value

a) Physicochemical properties (weight variation, hardness, friability, disintegration time, dispersion fitness and *in-vitro* drug release)

For weight variation, each formulation run, 20 tablets were taken and weighed carefully with an analytical balance. Standard deviation, minimum, maximum, and mean weight were all calculated.

Six tablets were taken from each run to test the tablets` hardness, forces required to break the tablet (in kilopond "kp") were measured using a hardness tester.

To check the friability, 10 tablets from each formulation were dedusted and accurately weighed, and they were put inside the drum of the friability tester. The instrument was then started at 25 rpm for 100 rotations. Tablets were removed after the completion of the 100 rotations, carefully dedusted, and then weighed. The percentage of weight loss was calculated using the following equation:

$$Friability\ (\%) = \frac{(Initial\ weight - Final\ weight)}{Initial\ weight} \times 100$$

For disintegration test, six tablets from each formulation run were taken and placed in the disintegration test apparatus to test disintegration. Water at 20-25°C was used as the media for the test. The minimum, maximum and mean disintegration time were recorded.

Two tablets were taken and placed in 100 ml of water from each run to perform the dispersion fitness test, then stirred until completely dispersed, and then poured through a 710 μm sieve. Formulations with the best physical performance observed from the above-mentioned tests were used to study the *in-vitro* drug release from formulations. Six tablets from each of the selected runs were subjected to the dissolution test as per the basic parameters of the Ranitidine HCl tablet monograph on the USP39-NF34, 2016. After that samples were taken from each vessel and drug content was determined using UV-spectrophotometer. First, the standard solution was prepared by transferring 93 mg of Ranitidine HCl working standard to a 1000 ml volumetric flask, then dilute and filtered to obtain a final concentration of 0.00093% w/v. Samples were filtered and diluted to obtain a final concentration of 0.00093% w/v. The absorbance of standard solution and samples was measured at λmax of 314 nm, and purified water was used as a blank. The amount dissolved in samples was measured in comparison with the standard solution.

b) Statistical data analysis

All test results for all formulation runs were fitted into Design-Expert software (Design-Expert version 8.0.6.0, Stat-Ease, Minneapolis, USA). Analysis of variance (ANOVA) was used to validate the design. Interaction plots, three-dimensional (3D) response surface plots, and cube graphs were sometimes constructed to simplify the relationship between the dependent and independent variables and their interaction. The F test and probability value (p-value) were also calculated to compare variance and determine significance, respectively. For all cases, a p-value of less than 0.05 indicates that the model terms are significant.

RESULTS AND DISCUSSION

i) Evaluation of taste masking trials:

All the used taste-masking techniques for the API raw material showed a significant effect on masking the bitterness of the API, which varied with changing the used material type, concentration, and method. The degree of taste masking with solid dispersion technique ranged from "bitter" at Ranitidine to Eudragit E100 ratio of (1:1), to "fully masked" at Ranitidine to Eudragit E100 ratio of (1:4). The same aspect was used by Pavani and Makkena to mask the taste of Nizatidine to formulate an orodispersible tablet in which similar results were obtained [8]. Results also varied from "bitter" at Nizatidine to Eudragit E100 ratio of (1:1), to "not bitter" at Nizatidine to Eudragit E100 ratio of (1:4 and 1:5).

The results of taste masking by granulation revealed that calcium carbonate needs to be used at high concentrations to give a significant masking property. Ratios of the drug to calcium carbonate up to (1:4) resulted in a slight taste-masking degree, while higher ratios of (1:8) and (1:10) led to acceptable taste. In 2017, Sasikumar used calcium carbonate to mask the taste of sildenafil citrate to formulate a sildenafil citrate chewable tablet. The unpleasant taste of the sildenafil citrate was masked by the intra-granular addition of calcium carbonate, it was noticed that the degree of taste masking increases as the concentration of calcium carbonate increases [9].

As clearly observed in Table 3, the degree of taste masking with the inclusion complex formation by β-CD varied significantly with changing the concentration, method, and solvent type. The best results were obtained when using the kneading method with a drug to a β-CD molar ratio of (1:2), which led to acceptable

taste masking. On the other hand, the granulation method did not obtain acceptable results even with the molar ratio of (1:3), as the kneading method assures more mixing homogeneity and better complex formation with the drug. The granulation method using water as a solvent obtained the worst results, this might be because β-CD is sparingly soluble in water but slightly soluble in ethanol [10], which will not lead to good complexation with the drug when using water as a solvent. Kneading method was used by Jagdale to mask the taste of diltiazem HCl using β-CD with a molar ratio of (1:1) to formulate an orodispersible tablet [11]. The taste was partially masked (moderately bitter taste) with the used ratio. Taste masking with combined granulation and inclusion complex formation obtained acceptable taste masking, which the same result is obtained when using inclusion complexation alone with a drug to a β-CD molar ratio of (1:2) by kneading method. This confirms that calcium carbonate has no significant effect when used at ratios up to (1:4) even if combined with β-CD

ii) Influence of different factors on the physical properties of the formulated tablets:

From the data revealed in Table 4, the model of the tablet's weight variation is significantly affected by the used manufacturing method and diluent type, along with the used disintegrant level. Although weight variation results for all formulations were acceptable, it can be noticed that the worst results (higher RSD %) were obtained when using mannitol as diluent. The highest RSD% (2.06%) was recorded for F1 which is composed of mannitol as a diluent, CCS as disintegrant with a concentration of 10%, and manufactured by direct compression. While the lowest RSD% (0.70%) was recorded for F9, followed by F14 and F16 (0.76% and 0.81%; respectively), where MCC was used as the diluent and wet granulation was the manufacturing method.

Moreover, it can be observed that the RSD% is increased as the disintegrant concentration increases when the direct compression method is used. Also, RSD% was found to increase in most formulations prepared by the direct compression method instead of wet granulation as observed in Figure 1.

As a general concept, the weight variation is highly correlated to the flow properties and particle size uniformity of the powder. Therefore, it must be aimed when tableting a powder that it can be dosed quickly and consistently into the dies of the compression machine. This explains why tableting often is preceded by a granulating process to give the feed material better flow characteristics than the physical mixture [12].

Table 3: Taste evaluation of Ranitidine HCl raw material after taste-masking trials

Trials	Volunteers						Average evaluation
	V1	V2	V3	V4	V5	V6	
Pure drug	5	5	5	5	5	5	5
T1	3	4	3	3	4	4	3.5
T2	2	3	4	4	2	2	2.8
T3	2	3	1	1	3	3	2.2
T4	1	1	2	1	2	1	1.3
T5	4	3	4	4	4	3	3.7
T6	3	4	4	4	4	3	3.7
T7	3	2	2	3	4	4	3.0
T8	3	2	1	1	3	1	1.8
T9	1	3	2	1	3	2	2.0
T10	2	3	3	2	4	4	3.0
T11	2	1	1	3	2	3	2.0
T12	3	4	4	4	2	4	3.5
T13	4	2	2	3	4	3	3.0
T14	2	2	1	2	3	2	2.0

Table 4: Weight variation, hardness, and friability results for the tablets formulations

Formula	Weight Variation				Mean Hardness (kp)	Friability (%)
	Min (mg)	Max (mg)	Mean of 20 tabs (mg)	RSD%		
F1	963	1090	995	2.06	2.53	2.01
F2	972	1035	1005	1.28	4.00	0.54
F3	969	1017	988	1.29	4.06	0.61
F4	962	1013	994	1.24	4.00	3.44
F5	973	1030	1002	1.00	4.18	1.53
F6	974	1038	995	1.19	8.41	0.49
F7	975	1005	993	0.89	6.44	0.86
F8	971	1032	1001	1.46	4.54	0.36
F9	963	1002	991	0.70	3.50	0.86
F10	965	1010	984	1.04	6.06	1.20
F11	958	1024	992	1.25	4.77	0.04
F12	971	1014	992	0.91	6.95	0.21
F13	968	1017	995	1.18	9.05	0.12
F14	977	1010	991	0.76	4.26	0.31
F15	965	1044	997	1.62	2.86	5.63
F16	963	1001	986	0.81	6.38	0.25

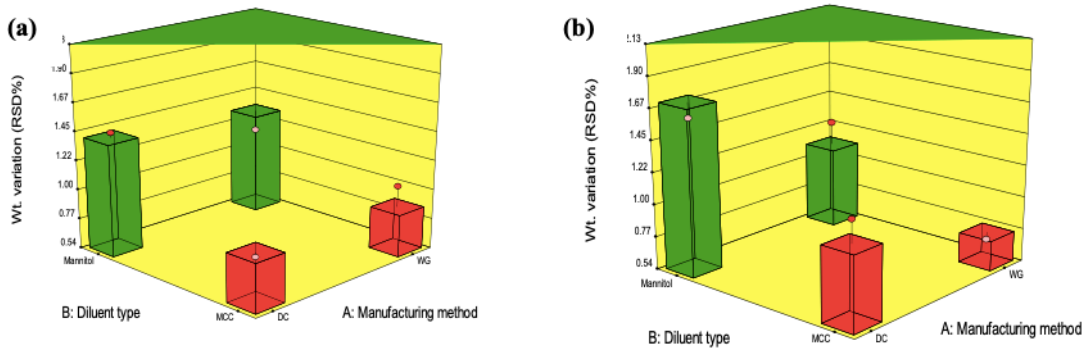

Figure 1: The influence of manufacturing method and diluent type on weight variation at disintegrant levels of (a) 2% and (b) 10% in Ranitidine dispersible tablets

The factors that have a significant influence on the tablet's hardness are the disintegrant level and manufacturing method, as noticed in Table 4. The diluent type also has a significant influence when combined with these two factors.

Figure 2 illustrated that hardness results were decreased when the disintegrant level increased from 2% to 10%. A marked difference is observed when using mannitol with different manufacturing methods. The hardness is highly increased when using the wet granulation method with mannitol. On the other hand, hardness was not changed markedly, when using MCC with the wet granulation method. Unlike the finer powder of mannitol, MCC 102 has high compactibility when used as a dry powder without the need for granulation [13]. This explains the non-significant change observed when MCC is used with wet granulation. The fine powder content increases, when the used disintegrant level is increased. This also explains the inversely proportional relationship between hardness and disintegrant level. This is similar to the results obtained by Mehta [14], where sodium starch glycolate was used as a tablet disintegrant. The tablet hardness decreased when disintegrant concentration increased.

The manufacturing method was found to be the only factor that significantly influenced tablet friability (Table 4). As observed in Figure 3, better friability results were obtained when using the

wet granulation method. The worst results of all formulations were obtained when using the direct compression method and high disintegrant levels (F1, F4, F5, and F15). This is due to fact that wet granulation results in less fine powder content within the blend and enhances bonding upon compression [15]

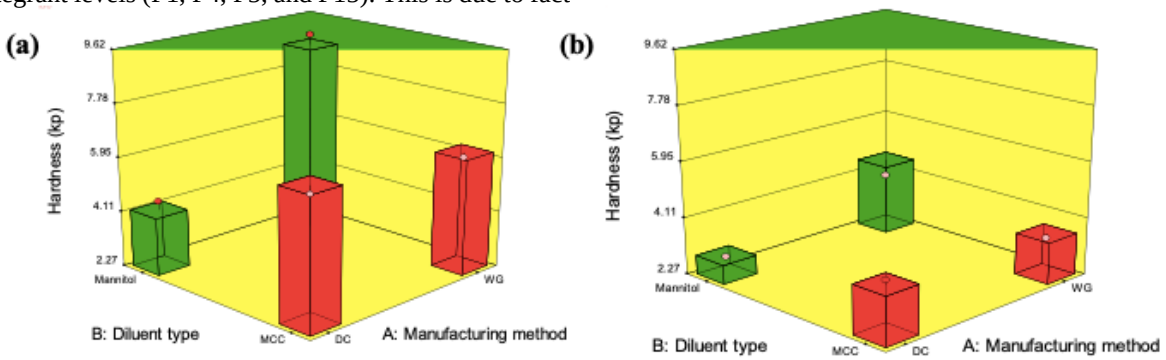

Figure 2: The influence of manufacturing method and diluent type on the hardness at disintegrant levels of (a) 2% and (b) 10% in Ranitidine dispersible tablets

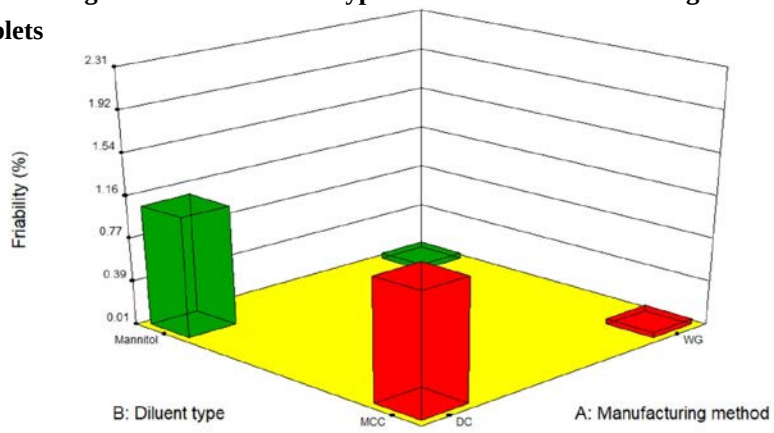

Figure 3: The influence of the manufacturing method on the friability of the formulated Ranitidine dispersible tablet at a disintegrant level of 2%

Table 5: Disintegration time and dispersion fitness results for the tablets formulations

Formula	Disintegration Time (minutes)			Dispersion fitness
	Min.	Max.	Mean of the 6 tablets	
F1	0.32	0.48	0.38	Pass
F2	0.42	0.50	0.58	Pass
F3	0.53	0.97	0.79	Pass
F4	0.25	0.33	0.28	Pass
F5	0.05	0.20	0.12	Pass
F6	1.00	1.47	1.19	Pass
F7	0.33	0.45	0.40	Pass
F8	2.33	4.17	3.06	Pass
F9	0.50	0.67	0.58	Pass
F10	0.50	1.33	0.92	Pass
F11	0.40	0.67	0.53	Pass
F12	0.17	0.58	0.36	Pass
F13	2.62	6.28	4.66	Pass
F14	0.30	0.42	0.36	Pass
F15	0.58	0.92	0.71	Pass
F16	0.25	0.42	0.33	Pass

Table 6: Disintegration time and dispersion fitness results for the tablets formulations

Formula	Disintegration Time (minutes)			Dispersion fitness
	Min.	Max.	Mean of the 6 tablets	
F1	0.32	0.48	0.38	Pass
F2	0.42	0.50	0.58	Pass
F3	0.53	0.97	0.79	Pass
F4	0.25	0.33	0.28	Pass
F5	0.05	0.20	0.12	Pass
F6	1.00	1.47	1.19	Pass
F7	0.33	0.45	0.40	Pass
F8	2.33	4.17	3.06	Pass
F9	0.50	0.67	0.58	Pass
F10	0.50	1.33	0.92	Pass
F11	0.40	0.67	0.53	Pass
F12	0.17	0.58	0.36	Pass
F13	2.62	6.28	4.66	Pass
F14	0.30	0.42	0.36	Pass
F15	0.58	0.92	0.71	Pass
F16	0.25	0.42	0.33	Pass

Reza conducted a study comparing the tablet properties when using MCC with direct compression and wet granulation methods [15]. His study also revealed that better friability and hardness were obtained when using the wet granulation method. Other supporting results were revealed from the study of Patra [16], who compared wet granulation and direct compression technologies on the formulation of *R. serpentina* root powder tablet. He concluded that the wet granulation process showed better blend flowability, compressibility, and compactibility compared to direct compression formulation.

A significant difference was noticed for tablet hardness results, which was higher when the wet granulation method was utilized. All factors applied have a significant influence on the disintegration time model (Table 5). As clearly seen in Figure 4, 5, and 6; the direct compression method was found to result in faster disintegration when compared to the wet granulation method (with fixing other factors). This is due to the large increase in particle size by wet granulation, which may reduce the efficacy of the disintegrant to absorb water into the tablet matrix [17]. Similar results were obtained by Zhao and Augsburger who evaluated the influence of granulation on the performance of disintegrants [17]. They found that the disintegration time of tablets is markedly increased when formulated with any class of wet granulated disintegrants. When MCC was used as the diluent, tablets showed faster disintegration than those containing mannitol as diluent. This is because MCC, unlike mannitol, has disintegrant properties in its nature and is sometimes used as a tablet disintegrant without adding other disintegrants [18]. As theoretically expected, disintegration time decreased when the disintegrant level increased. Croscarmellose sodium was found to yield better results than sodium starch glycolate with the same concentration (Figure 5 and 6).

These two disintegrants (along with another two types) were assessed for their effect on the release properties of spironolactone tablets by Rojas [19]. Sodium starch glycolate, although have a better swelling capability, is associated with moderate disintegration time, which may be due to the formation of a gel layer that delays disintegration. Faster compact disintegration was observed for croscarmellose sodium, which may be attributed to its moderate swelling propensity and the formation of weak compacts [19].

The drug release for all the chosen five formulation runs (F2, F11, F12, F14, and F16) was found to be within the stated pharmacopeial limit (NLT 80% Q). This is probably due to the

high water solubility of the drug [20]. Results illustrated in Figure 7 variated from the lower limit for F12 to the highest release for F14.

Generally, one of the main factors controlling tablet dissolution is the size of the granules. Dissolution of a tablet involves its disintegration into smaller particles from which the drug is released rapidly [21]. This explains why the dissolution results obtained from F11 and F14 were the highest among the five formulations, as these two formulations contain more disintegrant (10%) than F2, F12, and F16 (2%). Croscarmellose (along with other disintegrants) was studied for its effect with different concentrations on the dissolution of topiramate tablets. Priya found that the dissolution rate of topiramate tablets increased each time when the concentration of croscarmellose is increased from 2% to 3%, 4%, and 5% [22].

The same conclusion was also obtained by Setty [23], who studied the effect of different disintegrants, including croscarmellose sodium, on the dissolution of aceclofenac fast dispersible tablets. The dissolution rate was found to be proportional to the applied concentration of croscarmellose sodium, which was used at concentrations of 2%, 4%, 8%, and 12%.

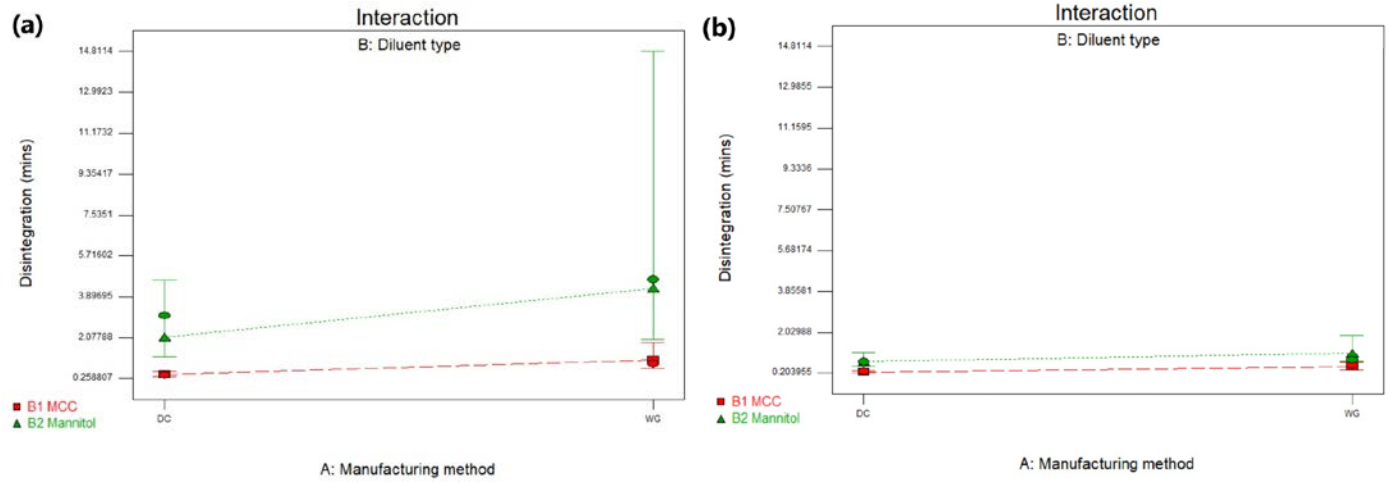

Figure 4: The influence of manufacturing method and diluent type on disintegration time of Ranitidine dispersible tablets using sodium starch glycolate as disintegrant at levels of (a) 2% and (b) 10%.

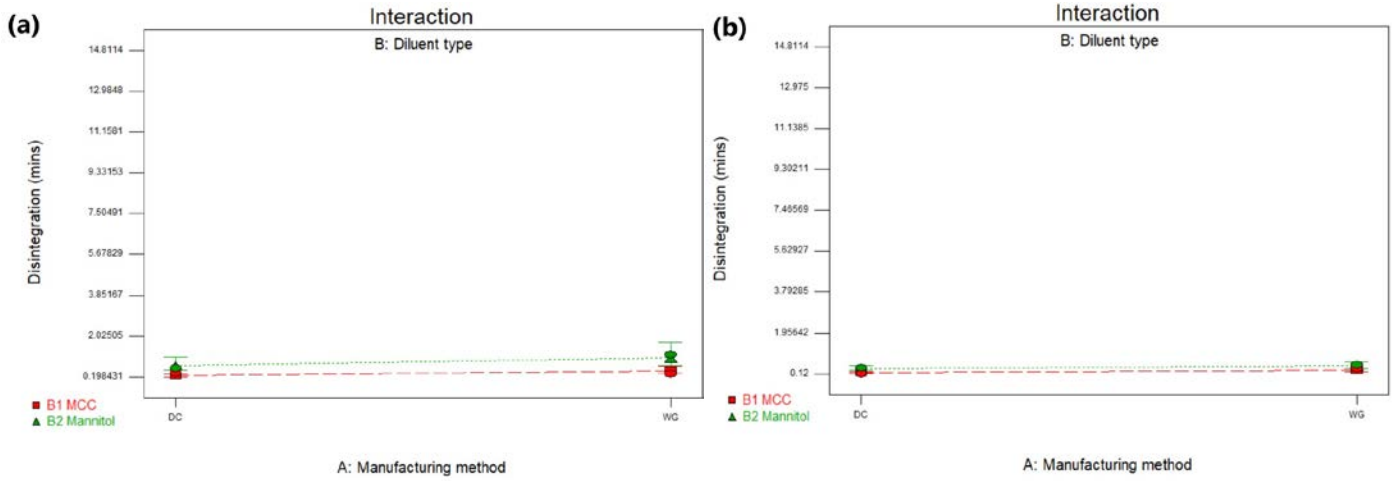

Figure 5: The influence of manufacturing method and diluent type on disintegration time of Ranitidine dispersible tablets using croscarmellose sodium as disintegrant at levels of (a) 2% and (b) 10%.

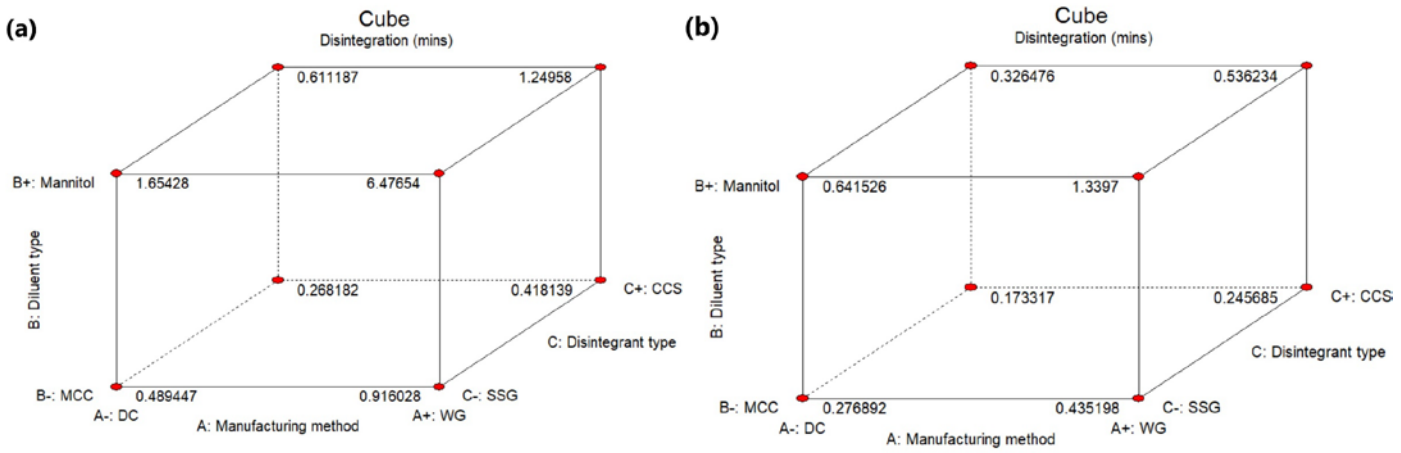

Figure 6: The influence of manufacturing method, diluent type, and disintegrant type on the disintegration time of Ranitidine dispersible tablets at disintegrant levels of (a) 2% and (b) 10%

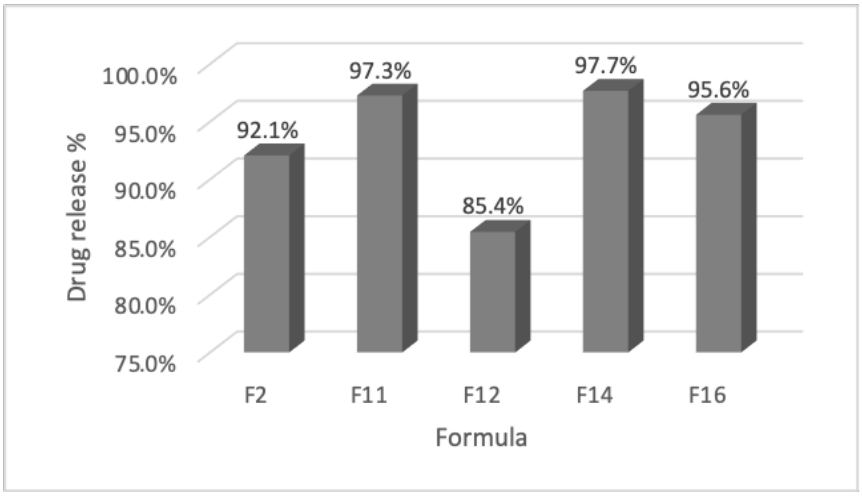

Figure 7: Drug release for runs F2, F11, F12, F14 and F16

CONCLUSION

Among all the techniques applied for taste masking of API, granulation with calcium carbonate (R. HCl: calcium carbonate ratio of 1:8) was found to be the method of choice to be implemented for this study. This method has a relatively low cost, acceptable taste-masking degree, and an easy manufacturing process.

All four factors implemented in this study affected at least one response significantly. The manufacturing method had a significant effect on all the responses. Diluent type and disintegrant level had a significant effect on all responses except friability, which is influenced only by the manufacturing method, while the disintegrant type influenced only disintegration time.

Croscarmellose sodium obtained better results than sodium starch glycolate with both direct compression and wet granulation methods. While MCC and mannitol resulted in good properties when implementing DC and WG methods, with low concentration and high concentration of CCS, respectively. Drug release is also increased by increasing the CCS level.

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Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Mohammed Shayoub and Zuheir Osman supervised all the work. Alaa E. Elawni and Mohammed Salih performed all experiments. Mohammed Salih helped with data analysis. Waleed Elballa wrote the manuscript and provided technical support. Alaa E. Elawni helped with editing and revising the manuscript. All authors read and approved the final manuscript

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