Al-Rafidain J Med Sci. 2024;7(1S):S15-23.
DOI: https://doi.org/10.54133/ajms.v7i(1S).867.iccpmu2024

Proceeding of the 5th International Conference, College of Pharmacy, Mustansiriyah University, Baghdad, April 2024 (ICCPMU2024)

Research Article

Online ISSN (2789-3219)

Formulation Variables Influencing the Development of Ketoconazole Gastroretentive Drug Delivery System

Moamin Fattah Al Hblawi*, Iman Sabah Jafar

Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq
Received: 30 April 2024; Revised: 16 June 2024; Accepted: 1 July 2024

Abstract

Background: Ketoconazole (KZ) is categorized as class II according to the Biopharmaceutics Classification System (BSC) classification, which shows a strong pH-dependent solubility where its solubility is enhanced under an acidic medium (pH below 3). This strong pH dependence results in unpredictable absorption and a wide range of bioavailabilities. ***Objective***: To prolong the gastric residence time of KZ's tablet to enhance KZ's solubility and hence its bioavailability for better therapeutic activity. ***Methods***: To prepare mucoadhesive tablets, we use both direct and wet granulation methods. We employed various evaluation tests to assess the prepared tablets. These tests encompass a range of assessments, including weight variation, hardness, thickness, friability, disintegration test, swelling study, mucoadhesive strength study, and in vitro drug release studies. ***Results***: The study found that polymer viscosity, as well as polymer concentration, have a significant effect on mucoadhesive strength and drug release, whereas diluent type has a non-significant influence on drug release. We selected Formula 7, which employs xanthan gum as a mucoadhesive polymer in a 1:1 drug polymer ratio, as the optimum formula because it provides an accepted physico-mechanical property and releases 87% of the drug over 8 hours. ***Conclusions***: Gastric mucoadhesive tablets may be an effective method of delivering active ingredients, as they provide a favorable environment that enhances their dissolution by extending their duration in the stomach, thereby increasing their bioavailability.

Keywords: Gastroretentive drug delivery system, Mucoadhesive tablet, Residence time.

متغيرات الصياغة التي تؤثر على تطوير نظام توصيل الدواء المعدي الكيتوكونازول

الخلاصة

الخلفية: يتم تصنيف الكيتوكونازول (KZ) ضمن الفئة الثانية وفقا لتصنيف نظام تصنيف الصيدلة الحيوية، والذي يظهر قابلية ذوبان قوية تعتمد على الأس الهيدروجيني حيث يتم تعزيز قابليته للذوبان تحت وسط حمضي (درجة الحموضة أقل من 3). يؤدي هذا الاعتماد القوي على درجة الحموضة إلى امتصاص لا يمكن التنبؤ به ومجموعة واسعة من التوافر البيولوجي. **الهدف**: إطالة وقت الإقامة في المعدة لقرص KZ لتعزيز قابليته على الذوبان وبالتالي توافرها الحيوي من أجل نشاط علاجي أفضل. **الطرق**: لتحضير أقراص اللصق المخاطي، نستخدم طرق التحبيب المباشرة والرطبة. استخدمنا اختبارات تقييم مختلفة لتقييم الأنظمة اللوحية المعدة. تشمل هذه الاختبارات مجموعة من التقييمات، بما في ذلك تباين الوزن، الصلابة، السماكة ، التفتيت واختبار التفكك، دراسة التورم، دراسة قوة اللصق المخاطي، ودراسات إطلاق الدواء في المختبر. **النتائج**: وجدت الدراسة أن لزوجة البوليمر وتركيزه لها تأثير كبير على قوة اللصق المخاطي وإطلاق الدواء، في حين أن النوع المخفف له تأثير قليل على إطلاق الدواء. اخترنا النموذج 7 ، التي تستخدم صمغ الزانثان كبوليمر لاصق مخاطي بنسبة بوليمر دوائي 1: 1 ، كصيغة مثالية لأنها توفر خاصية فيزيائية ميكانيكية مقبولة وتطلق 87٪ من الدواء على مدار 8 ساعات. **الاستنتاجات**: قد تكون أقراص اللصق المخاطي في المعدة طريقة فعالة لتقديم المكونات النشطة، لأنها توفر بيئة مواتية تعزز حلها عن طريق إطالة مدتها في المعدة، وبالتالي زيادة توافرها الحيوي.

* ***Corresponding author***: Moamin F. Al Hblawi, Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq; Email: muamn5@uomustansiriyah.edu.iq

Article citation: Al Hblawi MF, Jafar IS. Formulation Variables Influencing the Development of Ketoconazole Gastroretentive Drug Delivery System. *Al-Rafidain J Med Sci.* 2024;7(1S):S15-23. doi: https://doi.org/10.54133/ajms.v7i(1S).867.iccpmu2024

INTRODUCTION

The administration of drugs orally is still the most appropriate method for drug administration because of its painlessness, noninvasiveness, and ability to be self-administered by patients; moreover, oral medicines are frequently less expensive to produce and distribute than other forms of medication. However, oral drug administration presents several challenges, including a significant reduction in the number of drugs that reach the systemic circulation [1]. This can be attributed to the first-pass hepatic metabolism, as well as changes in absorption due to gastric content, gastrointestinal motility, and patient-related factors. Moreover, the absorption of drugs with a narrow absorption window decreases, unless their release occurs at the optimal location. To overcome these restrictions, researchers developed gastro-retentive drug delivery systems (GRDDS) [2]. GRDDS are progressive technologies recognized for improving drugs' gastric residence time, thereby increasing their bioavailability. Many GRDDS types have been developed; these may include swellable, floatable, magnetic, nano-fibrous, high-density, expandable, and mucoadhesive dosage forms. Among them, mucoadhesive drug delivery systems have gained considerable attention due to their unique characteristics. This type of GRDDS adheres to the mucous membrane coating the stomach, allowing extended residence time and improving drug absorption and bioavailability [3]. Furthermore, decreasing frequent administration of drugs with shorter half-lives leads to greater patient compliance. It also permits prolonged, stable drug release, qualifying local therapeutic properties in the stomach and upper small intestine [4]. This steady manner of drug release assures adequate activity at the targeted site, diminishes variations in plasma concentration of the drug, and, thus, regulates concentration-dependent adverse effects [5]. Numerous mucoadhesive dosage forms have been investigated, each with unique features and uses: mucoadhesive films, patches, gels, and mucoadhesive tablets [6]. Among these dosage forms, mucoadhesive tablets have acquired significant attention. These solid dosage forms are designated to adhere to the mucosal surface of the gastric and buccal mucosa and provide a controlled drug release. Higher local drug concentrations can be achieved by intimate contact of the tablet with the target absorbing layer, thus increasing the drug flux via the absorbing tissue [7]. Ketoconazole (KZ) is an imidazole broad-spectrum antifungal agent implemented in the treatment of topical as well as systemic fungal infections mainly produced by *Candida albicans*. It acts by inhibiting ergosterol synthesis, a key component of fungus cell membranes [8]. It is categorized as a class II drug according to BCS (low aqueous solubility) [9]. KZ solubility is highly reliant on the environment's pH and is considerably enhanced in an acidic medium. As the pH of the medium decreased below 3, KZ dissolution improved significantly, highlighting the crucial role of pH in KZ dissolution behavior [10]. KZ is a weak basic drug with a log P value of 4.35 and a pKa of approximately 6.51 [11]. Although KZ is an orally active drug, its medical use is limited due to its poor absorption due to fast gastric emptying [12]. The present study aims to formulate and *in vitro* evaluate gastroretentive mucoadhesive KZ tablets (as a model drug) to prolong the tablet residence time in the stomach and enhance KZ solubility by taking advantage of a gastric acidic medium.

METHODS

Materials

Ketoconazole (KZ) was obtained from Hefei Meyer Optoelectronic Technology Inc., China. Hydroxypropyl methyl cellulose K4M (HPMC K4M) and Hydroxypropyl methyl cellulose K15M (HPMC K15M) were purchased from Baoji Guokang Bio-Technology Co., Ltd., China. Xanthan gum (XG) and sodium alginate (Na Alg) were purchased from Shanghai Rizheng Chemical Technology Co., Ltd., China. The other used reagents were of analytical grade.

Tablets formulation

The study developed 14 formulas of mucoadhesive tablets using different drug-to-polymer ratios (1:1, 1:0.5, and 1:1.25). Different polymers and combinations were tested to assess their impact on formulation parameters (Table 1). All formulas (except F12) were prepared by mixing the drug, polymers, and other excipients (excluding the lubricant) for 15 minutes. The lubricant was then added and mixed for 5 minutes. Each final blend was compressed into a tablet using a 12 mm punch on a single-punch tablet machine (Riva, Germany) [13]. To prepare Formula F12, the wet compression method was used. The drug, polymer (XG), and diluent (Mannitol) were mixed by ascending weight for 15 minutes. Ethanol was then added to form a damp mass, which was granulated through a 1.25 mm sieve and dried in an oven at 40ºC for an hour. The dried granules were passed through a 0.630-mm sieve and mixed with talc and magnesium stearate for five minutes. Finally, the mixture was compressed into tablets using the same machine as previously described [14].

Pre-compressed mixture evaluation

We measured the angle of repose for physical mixtures using the fixed funnel and Petri dish technique. The sample powder was carefully poured through a fixed funnel into a Petri dish of known diameter. The angle of repose was calculated using the formula:

$$\text{Tan } Ø = h/r,$$

where Tan Ø represents the tangent of the angle of repose, h is the height of the powder cone and r is the

radius of the Petri dish [15]. To measure the Carr's index of each powdered formula, a carefully measured amount was placed into a 10 mL graduated cylinder to record its initial bulk volume (V0). The cylinder was then tapped until the volume stabilized (Vt). This process enabled the accurate determination of the formula's compressibility index [16]. The compressibility index was then calculated using the following equation:

$$\text{Compressibility Index} = ((V_0 - V_t)/ V_0) \times 100$$

Table 1: Composition of different tablet formulations

Formula Code	Ingredient (mg)									
	KZ	HPMC K 4M	HPMCK 15M	XG	Na-Alg	Talc	Mg stearate	Mannitol	Lactose	MCC
F1	200	200				10	10	80		
F2	200	100				10	10	180		
F3	200	250				10	10	30		
F4	200		200			10	10	80		
F5	200		100			10	10	180		
F6	200		250			10	10	30		
F7	200			200		10	10	80		
F8	200			100		10	10	180		
F9	200			250		10	10	30		
F10	200			200		10	10		80	
F11	200			200		10	10			80
F12w	200			200		10	10	80		
F13	200			100	100	10	10	80		
F14	200			150	50	10	10	80		

Tablet characterization

The thickness of the prepared tablets was measured using a digital micrometer caliper on three randomly selected tablets from each batch, and the average was calculated. To ensure the tablets can withstand mechanical shocks during manufacturing and distribution, a Monsanto hardness (Coslab, India) tester was used to measure the compression force required to break the tablets [17]. Tablet friability was evaluated using a friabilator (Guoming CS-2 Roche-type, China) operating at 25 rpm. Twenty tablets were weighed initially (W1), placed in the device, and subjected to 100 rotations. Afterward, the tablets were re-weighed (W2) to measure friability [18]. The fraction of weight loss was then calculated using the following equation:

$$\text{Friability Percentage} = (W_1 - W_2)/W_1 \times 100$$

W1 represents the initial weight, while W2 is the final weight.

Per the United States Pharmacopeia (USP) guidelines, each tablet must be weighed individually. To meet USP acceptance criteria, no more than two tablets should deviate by over 7.5% from the average weight, and no tablet should exceed double that percentage deviation [19].

Swelling study

The tablet was weighed on a glass cover slide, and the weight was recorded. It was then immersed in 500 mL of a 0.1N HCl (pH 1.2) solution. At 1, 2, 4, and 8-hour intervals, the tablet was removed, the excess fluid was blotted off with filter paper, and the tablet was weighed again. The swelling index, representing water uptake, was then calculated using a specific equation [20].

$$\text{Swelling Index} = (W_1 - W_0)/W_0 \times 100$$

where W_0 is the initial weight and W1 is the final weight at a specific time.

Ex vivo residence time assessment

Fresh sheep gastric mucosa was obtained, cut into small pieces, and firmly attached to a glass slide. A tablet was gently placed on the mucosa, and the setup was transferred to a beaker. After adding 100 mL of 0.1N HCl, the beaker was maintained at 37 °C and stirred at 100 rpm with a magnetic stirrer. The time taken for the tablet to detach from the mucosa was recorded [21].

Mucoadhesive strength assessment

A modified physical balance was used to measure the strength of mucoadhesiveness. A double-beam balance

was set up with fresh sheep gastric mucosa attached to a glass slide on the right side. As shown in Figure 1, we positioned a plastic cup beneath the mucosa and glued a tablet to it to ensure contact. The tablet was moistened before being attached to the mucosa. Water droplets were gradually added to a container on the left pan until the tablet detached from the mucosa. The weight of the water was then used to calculate the force required to detach the tablet using the following equation.:

$$N = W \times g/1000$$

where N is the bioadhesive force, W is the weight required for detachment of the tablet from the sheep gastric mucosa in grams, and g is the acceleration due to gravity at 9.81 m/sec² [21]. The mucoadhesive bond strength was calculated using the equation below [22].

Bond strength N/cm^2= Force of adhesion (F)/surface area (A).

Figure 1: Modified balance used for mucoadhesive strength determination.

In vitro drug release

Three separate tests were done using a USP dissolution apparatus type II (Paddle method) and a temperature of 37±0.5 °C to look at how the tablets released the drug. The tablets were placed into a 0.1N HCl solution (pH 1.2) of 900 mL, with the paddles spinning at a rate of 50 rpm. An aliquot of 5 mL was taken at precise time intervals and subsequently filtered through a syringe filter (0.45 µm). Each time we removed a sample, we substituted a fresh medium of 5 ml into the dissolution flask. The drug content was then examined spectrophotometrically at a wavelength of 269.5 nm and estimated using a previously constructed calibration curve [23].

Statistical analysis

The mean of three trials±SD was used to present the study outcomes. Statistical analysis was done employing a one-way ANOVA. Similarity factor analysis was performed for the dissolution test using the Microsoft Excel add-in D-D solver [24]. In one-way ANOVA, a result is considered significant if the *p*-value is <0.05, while in the similarity factor test, results are considered significant if f2 is lower than 50 and insignificant if f2 = 500-10 [25].

RESULTS

Results for flow properties and compressibility are shown in Table 2. The angle of repose of the tablet powder blend ranged from 22.4 to 32.66, and Carr's index ranged from 17 to 21). The hardness of the prepared tablets was in the range of 4.13±0.11 kg/cm^2 to 4.77±0.2 kg/cm^2. All tablets displayed a friability of less than 0.5%; tablets' thickness ranged from 5.19±0.03 mm to 5.47±0.06 mm; and tablets' weights ranged from 490.49 to 495.97 mg.

Table 2: Angle of repose and Carr's index

Formula Code	Angle of Repose	Carr's Index	Expected Flow
F1	26.57±0.93	20±0.15	Good/Fair
F2	24.57±0.56	20±0.22	Excellent/Fair
F3	32.66±0.35	21±0.33	Fair/Fair
F4	31.45±0.66	21±0.41	Fair/Fair
F5	26.57±0.90	16±0.28	good/good
F6	31.66±0.44	21±0.21	Fair/Fair
F7	32.25±0.85	19±0.15	Fair/Fair
F8	31.57±0.73	19±0.35	Fair/Fair
F9	31.6±0.34	16±0.41	Fair/good
F10	24±0.22	20±0.34	Excellent/fair
F11	26.4±0.65	21±0.18	Good/Fair
F12	30.4±0.82	21±0.36	Fair/Fair
F13	22.4±0.31	19±0.61	Excellent/Fair
F14	23.8±0.80	17±0.44	Excellent/Good

Table 3 demonstrates the physico-mechanical properties of prepared formulas. The obtained results, as shown in Table 3, reveal that all prepared formulas except F2 and F8 provide a residence time of more than 8 hours. Formulas F2 and F8 showed 5 and 6 hours, respectively. As shown in Table 4, the highest swelling index (260.07%) at 8 hours was observed with F7, which contains 200 mg XG. All formulas showed continual swelling through the eight-hour timeframe, except F2 and F8, which disintegrated faster than the others. The mucoadhesive strength of prepared formulas is shown in Table 4. Mucoadhesive strength ranged from 15.73 to 34.88 gm, and mucoadhesive force ranged from 0.154 to 0.34 N, while bond strength ranged from 0.00136 to 0.00301 N/cm^2. Formulas 4–6 were used to study the effect of polymer concentration on mucoadhesion strength. The mucoadhesive strength went up significantly (p-value: <0.0001) as the concentration of polymer went up.

Table 3: Physico-mechanical properties of prepared formulas

Formula Code	Friability (%)	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Mucoadhesion Time (hr)
F1	0.42	495.97±4.42	5.51±0.06	4.23±0.25	> 8
F2	0.34	492.05±6.32	5.32±0.025	4.13±0.11	5
F3	0.34	491.94±8.05	5.45±0.05	4.16±0.28	> 8
F4	0.36	492.88±6.47	5.4±0.025	4.64±0.2	> 8
F5	0.44	492.64±6.33	5.41±0.052	4.50±0.4	> 8
F6	0.40	493.59±6.33	5.47±0.06	4.77±0.2	> 8
F7	0.38	492.8±5.62	5.15±0.083	4.6±0.17	> 8
F8	0.36	492.89±4.97	5.19±0.03	4.23±0.25	6
F9	0.32	490.94±5.94	5.21±0.035	4.27±0.25	> 8
F10	0.38	491.34±5.27	5.33±0.02	4.233±0.25	> 8
F11	0.42	493.21±6.35	5.21±0.028	4.34±0.15	> 8
F12	0.34	492.33±5.45	5.2±0.015	4.37±0.24	> 8
F13	0.42	495.7 ±4.07	5.3±0.025	4.33±0.18	> 8
F14	0.42	493.21±5.91	5.41±0.052	4.23±0.25	> 8

Formula 6 had a higher mucoadhesive strength (38.09 gm) than Formula 4 (1:1) (34.45 gm) and F5 (1:0.5) (32.81 gm). As shown in Table 5, Formula 1 and F4 (which both have the same concentration of HPMC K4M and HPMC K15M) were used to study how the molecular weight of polymer affects mucoadhesion. The mucoadhesive strength went up significantly ($p<0.0001$) as the molecular weight of the polymer went up. For example, F4, which had 1:1 HPMC K15M, had a higher weight (34.45 g) than F1, which had 1:1 HPMC K4M and a weight of 18.77 g, as shown in Table 5. Formulas 4 and F7 were used to assess the effect of polymer type on mucoadhesive strength. A significant ($p<0.0001$) reduction in mucoadhesive strength was observed when changing the polymer type.

Table 4: Swelling index of prepared formulas

Formula Code	Initial Tablet Weight	Swelling Index (%)			
		1hr	2hr	4hr	8hr
F1	499	70.94	84.57	148.3	194.99
F2	497	76.28	98.99	116.7	-
F3	489	102.25	111.66	160.74	191.21
F4	491	98.57	103.67	138.7	211.2
F5	498	106.23	122.49	168.07	194.38
F6	504	99.206	158.14	200.6	248.21
F7	493	91.68	143.61	175.86	260.1
F8	495	128.89	151.92	167.88	-
F9	499	74.95	112.63	152.91	209.02
F10	493	87.83	93.10	128.4	196.96
F11	496	103.83	140.73	177.82	209.07
F12	494	105.47	164.78	209.51	228.22
F13	492	99.39	111.99	160.16	191.67
F14	488	104.3	163.93	213.12	241.6

Table 5: Mucoadhesion strength of prepared formulas

Formula Code	Mucoadhesion strength (gm)	Force of adhesion (N)	Bond strength N/cm^2
F1	18.77±0.68	0.184101	0.00163
F2	16.92±0.55	0.1659525	0.00147
F3	15.73±0.31	0.154344	0.00136
F4	34.45±0.41	0.3369081	0.00298
F5	32.81±0.27	0.3218334	0.00285
F6	38.09±0.4	0.373434	0.00330
F7	31.5±0.5	0.309445	0.00273
F8	30.89±0.67	0.3030309	0.00268
F9	34.88±0.31	0.34008	0.00301
F10	31.55±0.5	0.309342	0.00274
F11	29.34±0.55	0.259965	0.00230
F12	28.2±0.25	0.276642	0.00245
F13	22.97±0.55	0.225303	0.00199
F14	25.08±0.36	0.246231	0.00218

When HPMC K15 M in F4 was replaced by the same amount of XG in F7, mucoadhesive strength was reduced from 34.45 gm to 31.5 gm for F4 and F7, respectively, as demonstrated in Table 5. As shown in Figure 2, F4-F6, which contains HPMC K15M in different concentrations, was used to assess the effect of polymer concentrations on the drug release profile of prepared tablets.

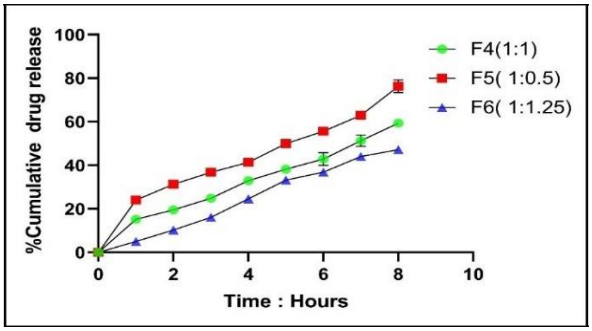

Figure 2: Effect of polymer concentration on drug release

Results showed that as the concentration of HPMC K15M increased, a significant decrease (similarity factor f2 = 46.225, 35.715) in drug release was observed where F5 (1:0.5), F4 (1:1) and F6 (1:1.25) drug-to-polymer ratios showed 76%, 69%, and 47% drug release over 8 hours, respectively. The molecular weight of the polymer shows a considerable effect on drug release, as confirmed by the significant (similarity factor f2: 47.563) reduction in drug release rates observed by replacing HPMC K4M in F1 by the same amount of F4 HPMC K15M, where F1 and F 4 showed (71.21%) and (59.38%) drug release, respectively, as shown in Figure 3.

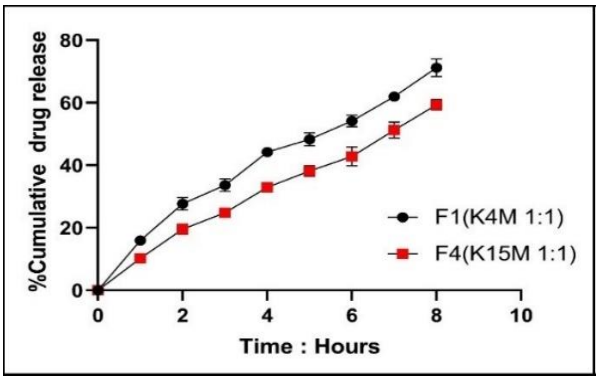

Figure 3: Effect of molecular weight on drug release.

Formulas 4 and 7, which contain the (1:1) drugs HPMC K15M and XG, respectively, were used to study the effect of polymer type on the drug release profile.

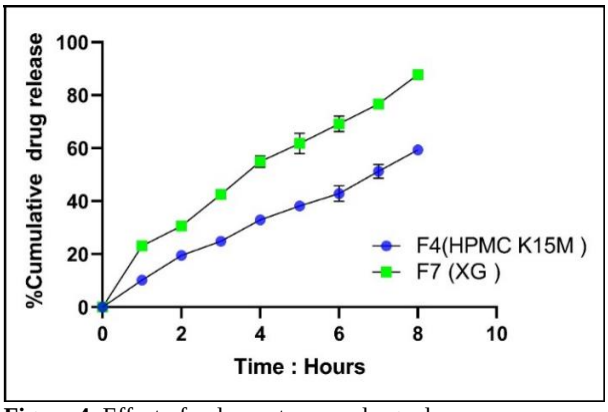

Figure 4: Effect of polymer type on drug release.

F7 (XG) showed significantly (similarity factor f2: 46.225) higher release compared to F4 (HPMC K15M), where (87%) and (59.83%) of the drug were released over 8 hours, as shown in Figure 4. Formulas 7, F10, and F11, which contain the same concentration of mannitol, lactose, and Avicel, respectively, were used to assess the influence of diluent on drug release from prepared tablets. F10 showed a non-significant increase (similarity factor f2 = 58.391 and 52.572) in drug release compared to F7 and F11, where 91.79%, 87.77%, and 85.46% of drugs were released over 8 hours. To study the effect of the preparation technique on drug release, F7 and F12, which were prepared by direct compression and wet granulation methods, respectively, were used. The results demonstrated that F12 showed a non-significant increase (f2 = 53.394) in drugs released compared to F7, where 89.37% and 87.77% of drugs were released for F7 and F12 over 8 hours, respectively. Formulas 7 (comprising XG 200 mg), F13 (comprising 100 mg XG and 100 mg Na Alg), and F14 (comprising 150 mg XG and 50 mg Na Alg) were used to study the effect of the addition of Na Alg as a secondary polymer. F7 showed significant (f2: 39.169, 48.750), a higher percentage of drug release (87.77%) compared to F13 (64.28%) and F14 (78.30%), as shown in Figure 5.

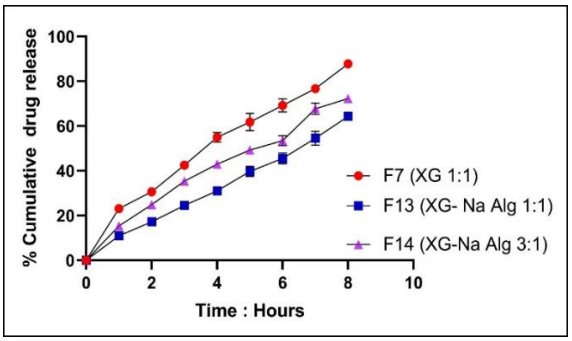

Figure 5: Effect of polymer combination on drug release.

DISCUSSION

The results revealed that formulations F1 to F14 exhibit the needed flow properties and acceptable compressibility, which make them appropriate for the tableting procedure. The measured repose angles specify satisfactory flow characteristics, which are critical for ensuring reliable filling of the die cavity throughout tablet manufacturing. Furthermore, the values obtained for Carr's index demonstrated that the compressibility of the mixtures ranges from acceptable to superior, which is an important parameter for tablet compaction [26]. The mechanical and physical characteristics of tablet formulations F1 through F14 were found to adapt to the USP standards. The tablets' ability to withstand pressure was measured. A friability test was also employed and the obtained results were within the USP standard of less than 1%. Tablet weight variation was within the acceptable range of ±5%, as USP guidelines state, evidencing the tablet's homogeneity. Tablets' thickness

acquired the necessary consistency for tablet production. The ex vivo residence time refers to the time required for thorough erosion and/or complete tablet separation from mucosal tissue [27]. Most formulas exceed 8 hours of residence time. This outcome could be linked to the high polymer concentrations encompassed in these formulations. These observations were in agreement with those of Sharma *et al*. (2015) [21]. In contrast, F2 and F8 demonstrated complete erosion faster than the other formulas. This is supported by the observations made by Agarwal *et al*. (2015), which revealed that formulas with lower polymer-to-drug ratios suffered from diminished mucoadhesive strength along with faster fragmentation of the tablets [28]. The swelling index offers a vital understanding of the expanding ability of the table, which is crucial to ensuring its retention in the stomach for an extended period and hence providing the required sustained drug release [29]. The highest swelling index was observed with F7 (containing KZ:XG 1:1). This could be attributed to easy polymer hydration as well as rapid swelling characteristics compared to other polymers [30]. Alternatively, F2 and F8 showed fragmentation before 8 hours, which could be due to their lower polymer concentrations [31]. *In vitro,* mucoadhesion strength tests are the most common and convenient methods to assess the mucoadhesive properties of candidate formulations [32]. The data presented in Table 5 displays that F6 had significantly higher mucoadhesion (p<0.0001) as compared to F4 and F5. It was observed that increasing HPMC K15M concentration led to potentiate mucoadhesion. This could be attributed to enlarged surface roughness and bigger pores within the matrix, resulting in higher chain flexibility and more free macromolecular chains capable of diffusing the mucus layer [33, 34]. The results showed a meaningfully better mucoadhesion (p<0.0001) strength with F4, having a higher molecular weight (HPMC K15M) compared to F1 (HPMC K4M). This is justified by the improved entanglement of the polymer chain through mucin produced by HPMC K15M. Comparable results are seen with those reported by Kumar *et al*. [35]. It was discovered that F4 containing HPMC K15M showed a higher significant ($p < 0.0001$) mucoadhesion strength compared to F7, which includes XG. The higher number of hydroxyl groups in HPMC may justify this result by enhancing its ability to form hydrogen bonds with mucus, a crucial step in the mucoadhesion process [36]. A comparable result was reported by Dalvadi *et al*. [37]. The results, as shown in Figure 3, confirmed that the concentration of HPMC K15M in the formula had an important influence on the amount of drug released. This discovery was reinforced by the similarity factor of dissolution, which was calculated as f2 = 46.225, 35.715. Interestingly, F4 displayed a dissimilar release profile compared to F5 and F6. Comparable findings were observed by Jaipal *et al.,* who reported a notable reduction in drug release fraction following the increase in HPMC concentration in the formulas [38]. The decrease in drug release rate with higher polymer concentrations can be linked to establishing a more viscous gel layer upon hydration, which acts as a barrier, generating a more complex distribution path for drug molecules [39]. The faster release percentage is seen in F1 compared to F4, which contains the same drug polymer ratio of HPMC K4M and HPMC K15M, respectively, reinforced by a statistically significant (f2: 47.563) and as shown in Figure 3. Comparable outcomes have been made by Sultan et al., who informed of remarkable changes in drug release rates by varied HPMC grades, where HPMC K4M showed the maximum release rates. In distinction, the HPMC K15M is presented as the lowest [34]. This may be justified as higher-molecular-weight polymers produce a thicker gel structure when hydrated. The denser the gel, the slower the drug diffusion, leading to a milder drug release. Additionally, high-molecular-weight polymers have an advanced grade of entanglement and consequently, additional polymer bonds are essential to be cracked for the system to rupture or form pores for drug release [40]. The release profile exhibited by F4 is in contrast to F7 and shows a significantly higher fraction of drug release (similarity factor f2: 46.225), especially in the later stages of the measured time frame as shown in Figure 4. This observation lines up with the results of earlier studies by Akash et al., who justified that the more noticeable release seen in the XG-containing formula may be attributed to the initial burst release in acidic media (pH 1.2) that XG tends to display, a characteristic that is not present in HPMC matrices. This is because HPMC K15M gels slowly and doesn't depend on pH, which leads to a more controlled and steady release pattern, as explained in previous research [41]. The results revealed that including lactose in F10 led to a considerable increase in drug release, although the increase was not statistically significant. The F2 similarity factor (58.391 and 52.572) indicated that the dissolution profiles of the three formulas were similar. This observation is consistent with the results achieved by Jaafar *et al.,* who demonstrated that a formula containing lactose as a diluent resulted in higher drug release. Because lactose dissolves easily in water, pores form in the matrix. This lets the dissolution medium get through by creating channels, which improves drug release [42]. The results indicated that F12 exhibited a slightly more rapid drug release rate in comparison to F7. However, after conducting a similarity test (f2 = 53.394), it was determined that this difference was not statistically significant. Similar findings were also reported in a study by Ma'ali *et al*. [43]. As shown in Figure 5, Formula 13 and F14 exhibited slower drug release compared to F7, which exhibited a significantly faster release profile (f2: 39.169, 48.750). These results are comparable to those reported by Rashitha et al. in their study [44]. This finding may be justified by the fact that Na Alg grows protonated in the acidic environment and consequently, its electrostatic interface between the chains increases, eventually preventing the amount of drug release under the acidic condition of the stomach [45].

Conclusion

Gastric mucoadhesive tablets could be considered a promising dosage form for delivering active ingredients with pH-dependent dissolution behavior by prolonging the residence time at the site of absorption and hence enhancing their bioavailability.

ACKNOWLEDGMENTS

The authors thank the College of Pharmacy, Mustansiriyah University for its support throughout the study.

Conflict of interests

No conflict of interests was declared by the authors.

Funding source

The authors did not receive any source of fund.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

REFERENCES

1. Dan N, Samanta K, Almoazen H. An update on pharmaceutical strategies for oral delivery of therapeutic peptides and proteins in adults and pediatrics. *Children (Basel)*. 2020;7(12). doi: 10.3390/children7120307.
2. Sabar MH, Jaafar IS, Mohamed MBM. In situ gel as a platform for ketoconazole slow-release dosage form. *Int J App Pharm*. 2018;10(5):76-80. doi: 10.22159/ijap.2018v10i5.27849.
3. Vinchurkar K, Sainy J, Khan MA, Mane S, Mishra DK, Dixit P. Features and facts of a gastroretentive drug delivery system- A review. *Turk J Pharm Sci*. 2022;19(4):476-487. doi: 10.4274/tjps.galenos.2021.44959.
4. Kumar R, Islam T, Nurunnabi M. Mucoadhesive carriers for oral drug delivery. *J Control Release*. 2022;351:504-559. doi 10.1016/j.jconrel.2022.09.024.
5. Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state and future perspectives on gastroretentive drug delivery systems. *Pharmaceutics*. 2019;11(4). doi: 10.3390/pharmaceutics11040193.
6. Zahir-Jouzdani F, Wolf JD, Atyabi F, Bernkop-Schnürch A. In situ gelling and mucoadhesive polymers: why do they need each other? *Expert Opin Drug Deliv*. 2018;15(10):1007-1019. doi: 10.1080/17425247.2018.1517741.
7. Bernkop-Schnürch A. Mucoadhesive polymers: Basics, strategies, and trends. Concise Encyclopedia of Biomedical Polymers and Polymeric Biomaterials: CRC Press; 2017. p. 941-960. doi: 10.1081/E-EBPPC.
8. Dudhipala N, Ay AA. Amelioration of ketoconazole in lipid nanoparticles for enhanced antifungal activity and bioavailability through oral administration for management of fungal infections. *Chem Phys Lipids*. 2020;232:104953. doi: 10.1016/j.chemphyslip.2020.104953.
9. Kara DD, Bangera PD, Mehta CH, Tanvi K, Rathnanand M. In silico screening as a tool to prepare drug-drug cocrystals of ibrutinib-ketoconazole: A strategy to enhance their solubility profiles and oral bioavailability. *AAPS PharmSciTech*. 2023;24(6):164. doi: 10.1208/s12249-023-02621-9.
10. Fung M, Be Rziņš KR, Suryanarayanan R. Physical stability and dissolution behavior of ketoconazole-organic acid coamorphous systems. *Mol Pharm*. 2018;15(5):1862-869. doi: 10.1021/acs.molpharmaceut.8b00035.
11. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2017 Nov 8. doi: 10.1093/nar/gkx1037. [cited 15-6-2024].
12. Kataoka M, Fukahori M, Ikemura A, Kubota A, Higashino H, Sakuma S, et al. Effects of gastric pH on oral drug absorption: In vitro assessment using a dissolution/permeation system reflecting the gastric dissolution process. *Eur J Pharm Biopharm*. 2016;101:103-111. doi: 10.1016/j.ejpb.2016.02.002.
13. Jin H, Ngo HV, Park C, Lee BJ. Mucoadhesive buccal tablet of leuprolide and its fatty acid conjugate: Design, in vitro evaluation and formulation strategies. *Int J Pharm*. 2023;639:122963. doi: 10.1016/j.ijpharm.2023.122963.
14. Macho O, Gabrišová Ľ, Guštafík A, Jezso K, Juriga M, Kabát J, et al. The influence of wet granulation parameters on the compaction behavior and tablet strength of a hydralazine powder mixture. *Pharmaceutics*. 2023;15(8). doi: 10.3390/pharmaceutics15082148.
15. Patil S, Talele GS. Gastroretentive mucoadhesive tablet of lafutidine for controlled release and enhanced bioavailability. *Drug Deliv*. 2015;22(3):312-319. doi: 10.3109/10717544.2013.877099.
16. Chakraborty M, Ridgway C, Bawuah P, Markl D, Gane PAC, Ketolainen J, et al.Optics-based compressibility parameter for pharmaceutical tablets obtained with the aid of the terahertz refractive index. *Int J Pharm*. 2017;525(1):85-91. doi: 10.1016/j.ijpharm.2017.03.093.
17. Mohylyuk V, Bandere D. High-speed tableting of high drug-loaded tablets prepared from fluid-bed granulated isoniazid. *Pharmaceutics*. 2023;15(4). doi: 10.3390/pharmaceutics15041236.
18. Razzaq S, Hanif S, Syed MA, Iqbal J, Hassan SS, Raza SA, et al. Development and evaluation of mucoadhesive buccal tablet containing metronidazole for the treatment of periodontitis and gingivitis. *Pak J Pharm Sci*. 2018;31(5):1903-1910. PMID: 30150187.
19. Javed QUA, Syed MA, Arshad R, Rahdar A, Irfan M, Raza SA, et al. Evaluation and optimization of prolonged-release mucoadhesive tablets of dexamethasone for wound healing: In vitro-in vivo profiling in healthy volunteers. *Pharmaceutics*. 2022;14(4). doi: 10.3390/pharmaceutics14040807.
20. Hussain A, Syed MA, Abbas N, Hanif S, Arshad MS, Bukhari NI, et al. Development of an ANN optimized mucoadhesive buccal tablet containing flurbiprofen and lidocaine for dental pain. *Acta Pharm*. 2016;66(2):245-256. doi: 10.1515/acph-2016-0020.
21. Sharma OP, Shah MV, Parikh DC, Mehta TA.Formulation optimization of gastroretentive drug delivery system for allopurinol using experimental design. *Expert Opin Drug Deliv*. 2015;12(4):513-524. doi: 10.1517/17425247.2014.944861.
22. Li A, Khan IN, Khan IU, Yousaf AM, Shahzad Y. Gellan gum-based bilayer mucoadhesive films loaded with moxifloxacin hydrochloride and clove oil for possible treatment of periodontitis. *Drug Des Devel Ther*. 2021;15:3937-3952. doi: 10.2147/dddt.S328722.
23. Mohsin BM, Sabah IJ, Hamad MS, Hazem MJ, Furqan MA, Doaa ZA. Oily in situ gels as an alternative floating platform for ketoconazole release. *Int J Res Pharm Sci*. 2020;11(2):2638-2649. doi: doi.org/10.26452/ijrps.v11i2.2278.
24. Zeeshan F, Lin PY, Sheshala R. Application of similarity factor (f 2) and time required to drug release (t%) indicators for dissolution profiles comparison of paracetamol tablets. *Indian J Pharm Edu Res*. 2020;54(3). doi: 10.5530/ijper.54.3.114.
25. Jiang WZ, Cai Y, Li HY. Chitosan-based spray-dried mucoadhesive microspheres for sustained oromucosal drug delivery. *Powder Technol*. 2017;312:124-132. doi: 10.1016/j.powtec.2017.02.021.
26. The United State Pharmacopeia (USP) 30, NF28, 2010, USA: The United State Pharmacopia Convention Inc. 2010.
27. Grassiri B, Zambito Y, Bernkop-Schnürch A. Strategies to prolong the residence time of drug delivery systems on ocular surface. *Adv Colloid Interface Sci*. 2021;288:102342. doi: 10.1016/j.cis.2020.102342.
28. Agarwal S, Murthy RS. Effect of different polymer concentration on drug release rate and physicochemical

properties of mucoadhesive gastroretentive tablets. *Indian J Pharm Sci*. 2015;77(6):705-714. doi: 10.4103/0250-474x.174993.
29. Ammanage A, Rodriques P, Kempwade A, Hiremath R. Formulation and evaluation of buccal films of piroxicam co-crystals. Future J Pharm Sci. 2020;6(1):16. doi: 10.1186/s43094-020-00033-1.
30. McArdle R, Hamill R. Utilisation of hydrocolloids in processed meat systems. In: Kerry JP, Kerry JF, (Eds.), Processed Meats: Woodhead Publishing; 2011. p. 243-69. doi: 10.1533/9780857092946.2.243.
31. Argin S, Kofinas P, Lo YM. The cell release kinetics and the swelling behavior of physically crosslinked xanthan–chitosan hydrogels in simulated gastrointestinal conditions. *Food Hydrocoll*. 2014;40:138-144. doi: 10.1016/j.foodhyd.2014.02.018.
32. Yu T, Andrews GP, Jones DS. Mucoadhesion and characterization of mucoadhesive properties. In: das Neves J, Sarmento B, (Eds.), Mucosal Delivery of Biopharmaceuticals: Biology, Challenges and Strategies. Boston, MA: Springer US; 2014. p. 35-58. doi: 10.1007/978-1-4614-9524-6_2.
33. Saurí J, Zachariah M, Macovez R, Tamarit JL, Millán D, Suñé-Pou M, et al. Formulation and characterization of mucoadhesive controlled release matrix tablets of captopril. J Drug Deliv Sci Technol. 2017;42:215-226. doi: doi.org/10.1016/j.jddst.2017.03.009.
34. Bayer IS. Recent advances in mucoadhesive interface materials, mucoadhesion characterization, and technologies. *Adv Mater Interfaces*. 2022;9(18):2200211 doi: doi.org/10.1002/admi.202200211.
35. Kumar BP, Kavitha P, Devi KJ. Formulation design and evaluation of mucoadhesive buccal tablets of nitroglycerin. *Int J Pharmacy Pharm Sci*. 2014;6(7):251-259.
36. Boddupalli BM, Mohammed ZN, Nath RA, Banji D. Mucoadhesive drug delivery system: An overview. *J Adv Pharm Technol Res*. 2010;1(4):381-387. doi: 10.4103/0110-5558.76436.
37. Dalvadi H, Patel J, Rajput G, Muruganantham V, Jayakar B. Development and characterization of controlled release mucoadhesive tablets of captopril. *Ars Pharmaceutica*. 2011;52(2):31-37.
38. Jaipal A, Pandey MM, Charde SY, Raut PP, Prasanth KV, Prasad RG. Effect of HPMC and mannitol on drug release and bioadhesion behavior of buccal discs of buspirone hydrochloride: In-vitro and in-vivo pharmacokinetic studies. *Saudi Pharm J*. 2015;23(3):315-326. doi: 10.1016/j.jsps.2014.11.012.
39. Newton AM, Lakshmanan P. Effect of HPMC - E15 LV premium polymer on release profile and compression characteristics of chitosan/pectin colon targeted mesalamine matrix tablets and in vitro study on effect of pH impact on the drug release profile. *Recent Pat Drug Deliv Formul*. 2014;8(1):46-62. doi: 10.2174/1872211308666140225143926.
40. Toews P, Bates J. Influence of drug and polymer molecular weight on release kinetics from HEMA and HPMA hydrogels. *Sci Rep*. 2023;13(1):16685. doi: 10.1038/s41598-023-42923-3.
41. Dadou SM, Antonijevic MD, Chowdhry BZ, Badwan AA, (Eds.), An overview of chitosan-xanthan gum matrices as controlled release drug carriers, IntechOpen. 2018. doi: 10.5772/intechopen.76038.
42. Sultana A, Aghajanzadeh S, Thibault B, Ratti C, Khalloufi S. Exploring conventional and emerging dehydration technologies for slurry/liquid food matrices and their impact on porosity of powders: A comprehensive review. *Comprehen Rev Food Sci Food Safety*. 2024;23(3):e13347. doi: doi.org/10.1111/1541-4337.13347.
43. Ma'ali A, Naseef H, Qurt M, Abukhalil AD, Rabba AK, Sabri I. The preparation and evaluation of cyanocobalamin mucoadhesive sublingual tablets. *Pharmaceuticals (Basel)*. 2023;16(10). doi: 10.3390/ph16101412.
44. Rashmitha V, Rao YM, Pavani S. Formulation and evaluation of fenoverine tablets. *Asian J Pharm Clin Res*. 2021;175-180. doi: 10.22159/ajpcr.2021.v14i4.40999.
45. Ghosal K, Adak S, Agatemor C, Praveeen G, Kalarikkal N, Thomas S. Novel interpenetrating polymeric network based microbeads for delivery of poorly water soluble drug. *J Polymer Res*. 2020;27(4):98. doi: 10.1007/s10965-020-02077-6.