Formulation Factors in influencing The Development of Gastro-retentive Mucoadhesive Tablets

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Abstract:

Ketoconazole (KZ) is a useful antifungal drug belonging to the imidazole group. its clinical use has been limited due to poor absorption, as it is primarily absorbed in the stomach and upper small intestine. Once the drug passes through the stomach via gastric emptying, its absorption significantly decreases, leading to reduced bioavailability.

This study aimed to develop gastro-retentive mucoadhesive tablets by testing different drug-polymer ratios and assessing their physical and functional characteristics. Nine formulations (F1-F9) were created as gastro-retentive mucoadhesive tablets using sodium alginate (Na Alg) and Carbopol 934 (Carb 934). The powder blend was tested for flow properties, and the resulting tablets were assessed for thickness, hardness, weight variation, friability, mucoadhesion time, swelling index, mucoadhesive strength, and in vitro drug release. Results revealed that Carb 934's high molecular weight and cross-linking promote prolonged mucoadhesion, leading to extended drug release. Formulations with higher Na Alg contents demonstrated more swelling but less mucoadhesion time than those containing Carb 934. Together, Carb 934 and Na Alg provided controlled drug release due to the balanced properties of the polymers. This study explored mucoadhesive gastro-retentive tablets of ketoconazole, which showed enhanced gastric retention and extended release. These properties are expected to improve the drug's absorption and bioavailability, potentially offering a more effective therapeutic option.

Keywords: Ketoconazole; Gastro-retentive drug delivery; Mucoadhesive tablet

تعزيز توصيل الكيتوكونازول من خلال تطوير تركيبة جديدة من الأقراص اللاصقة المخاطية المعوية

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خلاصة

يُعد الكيتوكونازول دواءً مضادًا للفطريات ينتمي إلى مجموعة الإيميدازول. ومع ذلك، فإن استخدامه السريري محدود بسبب امتصاصه الضعيف، حيث يتم إفرازه بسرعة بعد إفراغ المعدة. هدفت هذه الدراسة إلى تطوير أقراص لاصقة مخاطية معدية عن طريق اختبار نسب مختلفة من الدواء إلى البوليمر وتقييم خصائصها الفيزيائية والوظيفية. تم إنشاء تسع تركيبات كأقراص لاصقة مخاطية معوية باستخدام ألجينات الصوديوم وكاربوبول تم اختبار مزيج المسحوق لخصائص التدفق، وتم تقييم الأقراص الناتجة من حيث السمك والصلابة وتفاوت الوزن والهشاشة ووقت الالتصاق المخاطي ومؤشر الانتفاخ وقوة الالتصاق

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المخاطي وإطلاق الدواء في المختبر. أظهرت النتائج أن الوزن الجزيئي العالي والتشابك لكارب 934 يعززان الالتصاق المخاطي المطول، مما يؤدي إلى تحرر الدواء بشكل ممتد أظهرت التركيبات التي تحتوي على نسب أعلى من ألجينات الصوديوم (Na Alg) انتفاخًا أكبر ولكن وقتًا أقل للالتصاق المخاطي مقارنةً بتلك التي تحتوي على كاربوبول. وفر كاربوبول 934 وألجينات الصوديوم معاً إطلاقًا محكمًا للدواء نظرًا لخصائص البوليمرات المتوازنة. أظهرت هذه الدراسة أن الأقراص اللاصقة المخاطية المعوية قد تحسن بشكل كبير من التوافر البيولوجي للكيتوكونازول.

كلمات مفتاحية: كيتوكونازول، الأقراص الملتصقة بالغشاء المخاطي

1.Introduction

Ketoconazole (KZ) is an imidazole antifungal agent with a broad spectrum of activity. It is used to treat both topical and systemic fungal infections, particularly those caused by *candida albicans*. Its mechanism of action involves inhibiting the synthesis of ergosterol, an essential component of fungal cell membranes(1). It falls under class II drugs based on BCS classification (low water solubility).

The solubility of KZ greatly depends on the pH of the environment and is significantly improved in an acidic medium(2). The decrease in the medium's pH to below 3 resulted in a significant enhancement in KZ dissolution, emphasizing the important role of pH in KZ dissolution behavior(3, 4). Although KZ is an active drug orally, its treatment usage is diminished because of its limited absorption due to fast gastric emptying (5).

Thus, gastro-retentive drug delivery systems (GRDDS) were created to face these boundaries (6).GRDDS, are developed technologies made to prolong the settlement of drugs in the stomach, thus improving their effectiveness. There are various types of GRDDS, such as nano-fibrous, high-density, swellable floatable, magnetic, expandable, and mucoadhesive dosage forms. Mucoadhesive drug delivery systems, in particular, have garnered significant interest due to their distinctive properties (7).

These systems stick to the stomach's mucous membrane, prolonging drug retention, improve absorption, and enhance the bioavailability .They also allows for sustained and consistent drug delivery, indicating beneficial therapeutic effects in the stomach and upper small intestine. (8). The steadiness of the release of the drug ensures sufficient activity at the specific site, reduces fluctuations in the drug's plasma concentration, and therefore controls concentration-related side effects(9). Numerous types of mucoadhesive dosage forms have been studied, each possessing distinctive characteristics and applications. These include mucoadhesive films, patches, gels, and tablets with mucoadhesive properties (10).

Mucoadhesive tablets have garnered considerable interest in various dosage forms. These solid forms are designed to stick to the mucosal surface of the gastric and buccal mucosa, facilitating controlled drug release. Intimate contact of the tablet with the target absorbing layer can lead to higher local drug concentration, thereby increasing drug flux through the absorbing tissue. (11).

2.Materials and Methods

2.1 Materials

Ketoconazole (KZ) was sourced from Hefei Meyer Optoelectronic Technology INC, China. Carbopol 934 was procured from Baoji Guokang Bio-Technology Co., Ltd, China. Sodium Alginate was bought from Shanghai Rizheng Chemical Technology Co., Ltd, China. All materials used were of analytical grade.

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2.2 Methods

2.2.1 Tablets Formulation

The investigation included development of mucoadhesive tablets using various drug: polymer ratios (1:1, 1:0.5, and 1:1.25), as shown in Table 1. Various polymers alone and in combinations were used to assess their impact on several formulation parameters. This approach provided a comprehensive assessment of how these polymers influenced the characteristics of the formulations.

Table 1: Composition of prepared formulations

Formula Code	Contents (mg)					
	KZ	Na Alg	Carb 934	Talc	Mg st	Mannitol
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	100	100	10	10	80
F8	200	50	150	10	10	80
F9	200	150	50	10	10	80

2.2.2 Direct Compression Method

The drug, polymers, and other excipients (excluding lubricant) were accurately weighed and mixed by the geometrical dilution method for 15 minutes to ensure an even distribution of all the ingredients within the mixture. Afterward, the lubricant was added and mixed for 5 minutes. Finally, each formula's final blend which is for 20 tablets was compressed into tablets using a 12 mm punch and a single punch tablet machine (Riva, Germany)(12).

2.3 Evaluation of the flow Properties for Pre-compressed Powder

2.3.1 Angle of Repose

The angle of repose for physical mixtures was determined using the fixed funnel and petri dish technique. The procedure involved carefully pouring the sample powder into the fixed funnel, and observing its smooth movement through the fixed-diameter Petri dish. The angle of repose was then calculated using the specified equation:

$\tan Ø = h/r$,

where Tan Ø represents the tangent of the angle of repose, h represents the height of the cone that resulted after pouring, and r represents the fixed radius of the Petri dish (13)

2.3.2 Compressibility Index (Carr's index)

To evaluate the compressibility of each powder blend for each formulation, a carefully measured amount was placed into a 10 mL graduated cylinder, filling it to its initial bulk volume (V_0). Subsequently, the cylinder underwent a standard tapping, applying a consistent force, until the volume reached a constant state (V_t). This method facilitated the accurate determination of the compressibility index of the formulation.

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(14) The compressibility index was then calculated using the following equation:
Compressibility Index = $((V_0 - V_t)/ V_0)$ x100 …….. (14)

2.4 Assessment of Gasteroretentive Mucoadhesive Tablets

2.4.1 Tablet Thickness

The method utilized for evaluating the thickness of the manufactured tablets involved the random measurement of three tablets from each batch using a digital micrometre calliper. This was carried out to estimate the thickness of the tablets, and subsequently, the average thickness was determined based on the recorded measurements(15).

2.4.2 Tablet Hardness

To verify the ability of tablets to withstand mechanical shocks throughout the production, packaging, and transportation processes, they need to possess sufficient strength and hardness. The hardness of the tablets was evaluated using a Monsanto hardness tester to quantify the level of compression required to fracture the prepared tablet(16).

2.4.3 Tablet Friability

The assessment of tablet durability was performed using friability testing, utilizing a friabilator (Guoming CS-2 Roche-type, China). This involved a rotational device spinning at a speed of 25 rpm. Twenty tablets, initially weighed as W1 were subjected to 100 rotations inside the device, after which their weight (W2) was measured again (17)the fraction of weight loss was then calculated using the following equation:
Friability Percentage = $(W_1 – W_2) /W_1$ x100 (18)
W_1: initial weight
W_2 : end weight

2.4.4 Weight Variation

The guidelines of the United States Pharmacopeia (USP) require individual weighing of each tablet. To comply with the USP standards for approval, 20 tablets used, the average weight, of no more than two tablets should deviate by 5%, and no tablet should exceed twice that percentage deviation(19)

2.4.5 Swelling index

The weight of the tablet was initially measured by placing it on a glass cover slide, and the recorded data were obtained. After that, the tablet and cover slide were submerged in a beaker containing 500 mL of a 0.1N HCl (pH 1.2) solution. At intervals of 1, 2, 4, and 8 hours, the tablet and cover slide were carefully taken out of the solution and then weighed after removing the excess superficial fluid using filter paper. Finally, the swelling index, which indicates water uptake, was determined using the following equation. (20)
Swelling Index = $(W_1 – W_0) / W_0$ x100
W_0: initial weight
W_1: end weight at a specific time

2.4.6 Mucoadhesion Time studies

Fresh sheep gastric mucosa was obtained from a local butcher in Baghdad city. The specimen was sliced into small segments and firmly affixed to a glass slide. Gentle pressure was applied to position the tablets on the mucous membrane before transferring them to a beaker. Then, 100 mL of 0.1N HCl were added into this beaker, and the resulted mixture was kept at a constant temperature of 37°C while being stirred continuously for 8 hours using a magnetic stirrer at 100 rpm. The period for the tablets to detach was noted (21).

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2.4.6 Mucoadhesive Strength Assessment

A doublehand balance was used in the assessment of the strength of mucoadhesion by utilizing a modified physical balance. A fresh sheep gastric mucosa was originally obtained from a local butcher in Baghdad city. The mucosa then was sliced into small pieces and firmly attached to a glass slide using Plastic cable straps, which was then attached to the right side of the balance. Beneath the glass slide, a tablet was affixed to a plastic cup to ensure contact with the mucosa. Prior to the experiment, the tablet was moistened by 0.1 N HCL (Ph=1.2) and then affixed to the mucosa for 1 minutes. An amount of Water droplets was continuously added to a container, which had been placed on the left pan of the balance until the tablet detached from the mucosa. At this stage, the amount of water added to the container was measured and used to calculate the force required to detach tablet from the mucosa using the following equation:

$$N = W \times g / 1000 \quad (22)$$

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.

This method allowed accurate measurement of the mucoadhesive strength of the tablet.

The mucoadhesive bond strength was calculated as the equation below:

Bond strength (N/cm^2) = Force of adhesion (F) / surface area (A) (23).

2.4.7 In vitro drug Release Assessment

The drug release characteristics of the tablet were examined in triplicate using a USP dissolution apparatus, type II (Paddle method) at a temperature of 37±0.5°C. The tablets were placed in a 900 mL solution of 0.1N HCl (pH 1.2), with the paddles rotating at a speed of 50 rpm. At specific intervals, a 5 mL sample was collected and filtered through a filter syringe (0.45µm). Following each sample collection, 5 mL of fresh medium was introduced into the dissolution flask. The drug concentration was then determined spectrophotometrically at a wavelength of 269.5 nm and quantified using a previously prepared calibration curve(24).

2.4.8 Statistical Analysis

The mean of three trials ± standard deviation (SD) was used to present the study outcomes. Statistical analysis was done employing one-way ANOVA. Similarity factor analysis was performed for the dissolution test using DSOLVER Add in within Microsoft excel (25, 26).

3. Results and discussion

3.1 Angle of repose and Carr's index

According to the obtained results as shown in Table 2, it is evident that formulations F1 - F9 are suitable for the tablet manufacturing process. They demonstrate satisfactory flow properties: angle of repose (from 23.8 to 32.25) and compressibility Index (from 17 to 21), both of which are crucial factors in this process. Furthermore, Carr's index values are within an acceptable range, indicating that these formulations will compact effectively into tablets. These pre-compression parameters are essential for evaluating the readiness of a powder for tablet processing, and in this instance, formulations F1- F9 meet the criteria. They are well-matched for the planned tableting procedure

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Table 2: Pre-compressed Powder Mixture Evaluation

Formula no.	Angle of Repose	Carr's index	Expected Flow
F1	23.8	17	Excellent/good
F2	32.25	19	Fair/Fair
F3	26.4	21	good/fair
F4	31.45	21	Fair/Fair
F5	31.6	16	Fair/good
F6	26.4	21	good/fair
F7	23.8	17	Excellent/good
F8	31.57	19	Fair/Fair
F9	26.4	21	good/fair

3.2 Evaluation of prepared Tablets:

3.2.1 Hardness, Thickness, weight variation, and friability

Table 3 demonstrates the physical and mechanical properties of prepared formulas, the obtained results for tablet formulas including the hardness, thickness, weight variation, and friability as shown in Table 3 demonstrate that these formulas exhibit mechanical and physical characteristics that meet the standards. Weight variation is an official test according to pharmacopeial standards, ensuring uniformity in dosage units. Hardness and friability, while important for evaluating tablet quality, are not official tests. They are, however, crucial for assessing the mechanical strength and durability of the tablets, which are critical for practical use. The tablets' hardness, is a crucial indicator of their resistance to pressure, ensuring robustness during handling and shipping, while still maintaining a level that does not impede proper dissolution (27). Formulas 1- F3 in which Na alginate was used as a mucoadhesive polymer provide lower tablet hardness compared to F4-F9 which showed a hardness value of more than 10 kg/cm^2. This may be related to the presence of Carb P934 in all of these formulas which have a binding ability (28). All prepared formulas showed a % friability value of less than 0.5%. The tablet's friability, which indicates its abrasion resistance, is within the USP standard of less than 1%, hence indicating strong tablet integrity (29)The weight variation of all formulas demonstrated the tablet's mass uniformity and dosing precision since it remained within the acceptable range of ±5% as per USP guidelines, ensuring consistent therapeutic effectiveness (30)The tablet's thickness, ranging from 5.20±0.025 mm to 5.4±0.06 mm, adheres to the necessary uniformity for tablet production according to pharmacopeial methods. (19).

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Table 3: Physico-mechanical properties of prepared formulas.

Formula Code	% Friability	Weight Variation	Thickness	Hardness	Mucoadhesion Time
F1	0.40	496.21 ± 5.46	5.21±0.028	4.64±0.2	4hr.
F2	0.37	492.7 ± 3.88	5.3±0.025	4.50±0.4	3hr
F3	0.41	488.21 ± 6.35	5.21±0.028	4.77±0.14	4hr
F4	0.42	495.97 ± 4.54	5.51±0.06	>10	> 8hr
F5	0.34	491.05 ± 5.82	5.32±0.025	>10	>8hr
F6	0.38	495.8 ± 5.62	5.15±0.083	>10	> 8hr
F7	0.36	492.88 ± 5.27	5.4±0.06	>10	>8hr
F8	0.36	494.89 ± 5.97	5.20±0.025	>10	>8hr
F9	0.38	497.94 ± 5.94	5.21±0.035	>10	>8hr

3.2.2 Swelling index

When comparing different formulations, the early swelling time point is particularly important for the action of gastroretentive tablets. Rapid initial swelling is crucial as it helps the tablet expand quickly, allowing it to maintain its position in the stomach and prolong its retention time. This early swelling is especially significant in formulations containing higher sodium alginate content, which enhances the tablet's ability to stay in the gastric environment, supporting its intended gastroretentive function(31) The swelling index plays a significant role in evaluating mucoadhesive gastroretentive tablets. It offers valuable information about the tablet's capacity to swell, which is crucial for ensuring its prolonged stay in the gastric region(32). Formulations with higher Na Alg ratios exhibit greater expansion compared to those with lower concentrations, as illustrated in Table 4. This observation may be attributed to the fact that Na Alg possesses a loosely cross-linked structure, contributing to its enhanced swelling capabilities (33). However, formulas with Na Alg disintegrate faster than the other formulas , which limits their swelling index assessment. Among the formulated tablets, those containing Carb 934 alone exhibited the lowest swelling index. For tablet formulations composed of a Carb 934 – Na Alg mixture, the swelling index study indicated that the rate of swelling was proportional to the sodium alginate content and inversely proportional to the Carbopol 934 content. This behavior can be attributed to the greater hydrophilic nature of sodium alginate compared to Carbopol, which results in a faster and more pronounced swelling effect. Similar results were observed in the study by Rahi et al(34).

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Table 4: Swelling index of prepared formulas

Formula Code	Tablet Weight	Swelling index %			
		1hr	2hr	4hr	8hr
F1	492	102.94188	125.56914	160.2966	-
F2	493	91.25755	115.99396	-	-
F3	499	116.2495	137.6564	175.7362	-
F4	491	60.57434	103.666	138.6965	211.2016
F5	495	52.2249	91.49	122.0723	160.3775
F6	489	65.20635	113.1349	143.5952	228.2143
F7	502	70.68357	123.6105	153.8621	220.070
F8	497	65.8889	113.9192	140.8788	211.204
F9	492	80.9499	134.6253	162.9058	279.018

3.2.3 Mucoadhesion time

Mucoadhesion duration of nine formulas (F1-F9) was evaluated, and the findings are summarized in Table 3. The results demonstrated that F1-F3 which employs Na Alg as a mucoadhesive polymer had a shorter mucoadhesion time (3-4 hrs.) compared to F4-F9 which comprises Carb 934 (> 8 hrs.) at a similar drug-to-polymer ratio accordingly. This aligns with the discoveries reported by J Yan et al. 2017, linking this outcome to the large molecular weight of Carb 934 and consequently a greater degree of cross-linking. Higher molecular weight denotes the dimensions and extent of the polymer chains comprising the material, thereby elongating the polymer chains inherently raises the overall mass of the molecule. The cross-linking refers to the formation of bonds between different polymer chains, creating a three-dimensional network that gives the polymer its unique properties, such as high viscosity and excellent gel formation capabilities. With a higher degree of cross-linking, the polymer chains form a dense network, leading to several significant effects including more controlled release of drug from polymer network (35).

3.2.4 Mucoadhesion strength

Table 5 demonstrates the mucoadhesive strength of prepared formulas.

3.2.4.1 Effect of polymer concentration

The impact of polymer concentration on mucoadhesion strength was studied using F1-F3. The results demonstrated that as the concentration of the polymer (Na Alg) increased, the mucoadhesion strength increased significantly (p-value: <0.0001), with F1, F2, and F3 showing mucoadhesion strengths of 38.45, 32.81, and 41.09, respectively. These results can be attributed to the ability of sodium alginate to form an in-situ gel with calcium ions present in gastric secretions, which enhances mucoadhesion through its gel-forming properties rather than surface tension effects. This is in contrast to Carbopol, which, due to its cross-linked structure, provides superior mechanical strength and prolonged mucoadhesion through entanglement with mucus (36).

3.2.4.2 Effect of polymer type

Formula 1 and F4 were implemented to evaluate the impact of polymer type on mucoadhesive strength. The results showed that F4, which contains Carb 934, exhibited

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significantly higher mucoadhesive strength (p-value: <0.0001) compared to formula F1, which contains Na Alg. Similar observations were obtained and justified by the rapid swelling and interpenetration of the polymer chains, leading to greater bioadhesion by Carb 934(37).

Table 5: Mucoadhesion strength of prepared formulas

Formula Code	Mucoadhesion Strength (g)	Force of adhesion (N)	Mucoadhesive Bond
F1	38.45±0.32	0.3771945	0.003338004
F2	32.81±0.27	0.3218661	0.002848373
F3	41.09±0.55	0.4030929	0.003567194
F4	45.36±0.75	0.4449816	0.00393789
F5	41.81±0.47	0.4101561	0.0036297
F6	49.09±0.35	0.4815729	0.004261707
F7	40.39±0.65	0.3962259	0.003506424
F8	42.25±0.72	0.4360545	0.003858889
F9	44.45±0.28	0.4152573	0.003674843

3.5 In vitro drug release

3.5.1 Effect of polymer concentration

Formula 4- F6, which contained different concentrations of Carb 934 were used to study the impact of polymer concentration on drug release from prepared tablets. The obtained results, as depicted in Figure 3, confirmed that the concentration of Carb 934 in the formula significantly impacted the amount of drug released where the drug release decreased significantly as the concentration of Carb 934 increased. This observation was supported by the calculated similarity factor of dissolution, denoted as f_2= 46.225, 35.715. Notably, F5 exhibited a distinct release profile of (59.122 %) compared to F4 and F6 (48.88% and 35.75%) . Similar findings were reported by Y Xuan et al 2020, who observed a significant decrease in drug release with an increase in Carb 934 concentration in the formulas. This limited drug release could be attributed to increased viscosity due to solvent penetration into a dense network, which restricts drug release (38, 39).

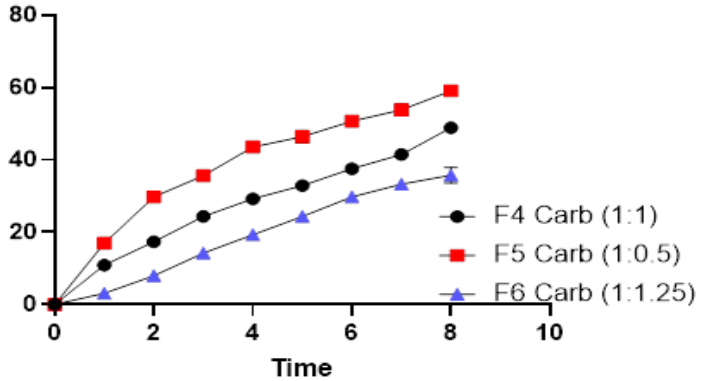

Figure 1 : release profile in 0.1N HCl at 37°C (Effect of polymer concentration)

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3.5.2 Effect of type of polymer

Formula 1 and F4, which have the same concentration of Carb 934 and Na Alg, were utilized to examine the impact of polymer type on drug release behavior as shown in Figure 2. While F1 disintegrated after only 4 hours, F4 continued to release the drug gradually over a period of 8 hours. The rapid disintegration of the Na Alg tablet may be associated with the fact that when Na Alg comes into contact with fluids, the alginate absorbs water and expands, creating stress within the tablet structure and causing it to break apart(40, 41).

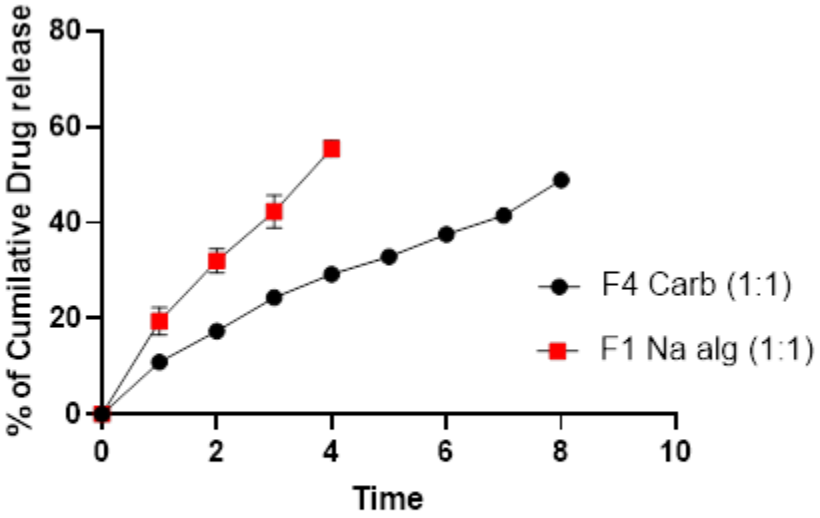

Figure 2 :release profile in 0.1N HCl at 37°C

Effect of polymer type

3.5.3 Effect of polymer combination

Formula 7- F 9 were used to evaluate the effect of the combination of polymers on drug release where F7, F8, and F9 which contain (Carb 100mg: Na Alg 100 mg) (Carb 150 mg: Na Alg 50 mg) and (Carb 50mg: Na Alg 150mg) respectively.

The results as shown in Figure 3 demonstrate a significant increase in drug release as the ratio of Na Alg in combination increased (as evidenced by f2 values of 48.345 and 37.520). This outcome could be possibly due to the water-soluble nature of Na Alg and its ability to form a gel layer , which undergoes dissolution and leads to the formation of pores and channels within the tightly cross-linked viscous gel layer. The penetration of the dissolution media within the matrix tablet allows the drug to diffuse out through the device (42).

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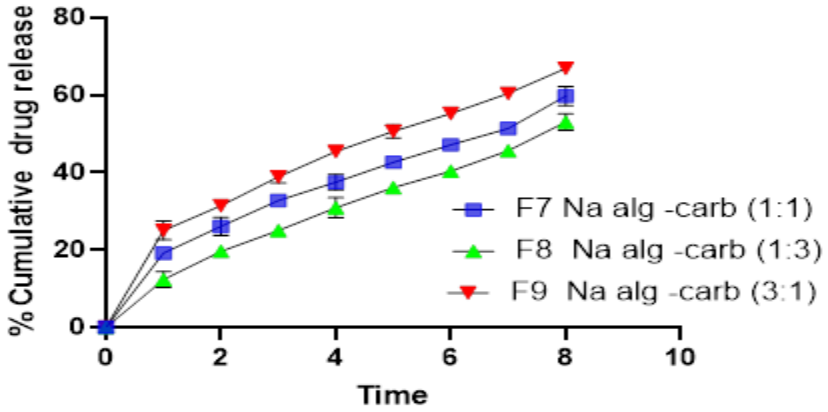

Figure 3 :release profile in 0.1N HCl at 37°C

Effect of combination

4.Conclusion

In this study, nine different mucoadhesive gastro-retentive formulations were successfully prepared and evaluated using sodium alginate and Carbopol 934, either alone or in combination. The findings highlighted those formulations containing Carbopol 934 provided prolonged mucoadhesion and consistent drug release due to their high molecular weight and degree of cross-linking. Sodium alginate formulations, while offering greater swelling properties, showed shorter mucoadhesion times due to rapid tablet disintegration. However, combining Carbopol 934 and sodium alginate created a balanced drug delivery system that benefited from the properties of both polymers, leading to controlled and prolonged drug release. This was seen in F9, offering promising release profile and sufficient mucoadhesion force and time, offering more residence allowing opportunity for increased absorption, this approach may offer a promising strategy for improving the residence time of ketoconazole and potentially other drugs with similar challenges. Further studies could refine the formulations to optimize their therapeutic efficacy and bioavailability.

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