Formulation and Evaluation of Sustained and Raft Forming Antacid Tablet

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Abstract

Antacids have been widely used in the treatment of various gastric and duodenal disorders such as heartburn, reflux esophagitis, gastritis, irritable stomach, gastric and duodenal ulcers. A pH-responsive of bi-polymer of sodium alginate and pectin have been studied as raft-forming polymers using sodium bicarbonate and calcium carbonate as gas-generating and calcium ion sources. The aim of study was to formulate and evaluate mono and bilayer tablets of floating and sustained release antacid delivery systems using sodium carboxy methyl cellulose as a gel forming substance, calcium and magnesium carbonate as sources of acid neutralizing and carbon dioxide gas generators agents upon contact with acidic solution. The effect of the formulation contents on the buoyancy has been investigated. In addition to, the antacid activities of intact and pulverized tablets have been studied. The result obtained showed that the buoyance is remarkably affected by the percentages of sodium carboxy methyl cellulose and carbonates salts. All formulas of mono and bilayer tablets revealed sustained action of acid neutralization and raft formation. Besides, bilayer tablets showed a significant and higher level of acid neutralizing capacity than monolayer tablets. Moreover, the pulverized of bilayer tablets exhibited significant and higher acid neutralizing capacity at raft than that at bulk of artificial gastric juice medium.

Keywords: Raft forming agent, Antacid, floating drug delivery, Acid neutralizing capacity, Sodium carboxy methyl cellulose.

تصييغ وتقييم أقراص مضادات حموضة مديدة وطافية

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الخلاصة

قد استخدمت مضادات الحموضة على نطاق واسع في علاج مختلف اضطرابات المعدة والاثني عشر مثل الحرقة ، ارتجاع المريء ، التهاب المعدة، المعدة العصبي ، قرحة المعدة و الاثني عشر. تمت دراسة استجابة البوليمرات الثنائية لألجينات الصوديوم والبكتين لتغير الأس الهيدروجيني على تشكل بوليمرات مكونة للطوف باستخدام بيكربونات الصوديوم وكربونات الكالسيوم كمصدر لتوليد الغاز ومصدر لأيونات الكالسيوم.

الغرض من الدراسة هو تحضير و تقييم أقراص أحادية وثنائية الطبقة مديدة وطافية من مضاد الحموضة باستعمال سليلوز الكاربوكسي مثيل الصوديوم كمادة مكونة للهلام واستخدام كربونات المغنيسيوم وكربونات الكالسيوم كمصادر لمعادلة الحامضية وعوامل مولدة لغاز ثنائي أوكسيد الكاربون عند ملامستها للمحلول الحامضي. تمت دراسة تأثير محتويات التصيّغ على انشطة الطفو ومضادة الحموضة. أظهرت النتائج أن قابلية الطفو تتأثر بصورة ملحوظة بنسبة سليلوز الكار بوكسي مثيل الصوديوم واملاح الكربونات. جميع الصيّغ للأقراص أحادية وثنائية الطبقة أبانت فعالية مديدة لمعادلة الحموضة وتكوين الطبقة الطافية. بجانب ذلك، الأقراص ثنائية الطبقة أظهرت مستوى عالٍ وذو اعتبار في قابلية معادلة الحموضة عن الأقراص أحادية الطبقة. علاوةً على ذلك، أظهر مسحوق الأقراص ثنائية الطبقة مستوى عالٍ وذو اعتبار في قابلية معادلة الحموضة عند الطبقة الطافية عنه في العمق وسط عصارة المعدة الصناعي.

الكلمات المفتاحية: عامل تكون الطفو، مضاد الحموضة، إطلاق دوائي يطفو على السطح، قابلية معادلة الحموضة، سليلوز الكار بوكسي مثيل الصوديوم.

Introduction

Gastric ulcer and gastroesophageal reflux are the most common disorders in one tenth of western's population [(1)]. The antacids probably used at the beginning of previous century once Celsus used neutralizing soils for treatment of gastric distress. The prim use of antacids as an ulcer curing agent started in 1856, when William Brinton used a combination of bicarbonate potash with bismuth to treat peptic ulcer. The scientific use of antacids to treat gastric ulcer was initiated in 1910 while the pronouncement of Schwarz prominent dictum, "no acid - no ulcer". In the next 50 years, antacids products were extensively used and grew further [(2)]. Antacids have been widely used in the treatment of various gastric and duodenal disorders such as heartburn, reflux esophagitis, gastritis, irritable stomach, gastric and duodenal ulcers.

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The carbonates and hydroxides of magnesium and aluminum have been extensively used as antacid in different combination ratios. As well as, they were incorporated to each other to prepare dry or wet gel that known as the layer lattice antacids. Furthermore, magnesium trisilicate, calcium carbonate and aluminum phosphate were also slightly used [3].

Gastro-retentive delivery systems have been used for more efficient treatment of local gastric diseases as well as to attain a high and more sustained therapeutic efficacy[4]. So far, floating system have been applied to prolong gastric retention time, increase of the drug absorption within the stomach, and improve the release rate of drug in the gastrointestinal tract[5, 6]. Buoyancy is the fact that determined by Archimedes. It is a state that the object with less density than that for a fluid will float in that fluid. More generally, Archimedes' principle based on that a fluid will exert an upward force on an object that immersed in and it equals to the weight of the fluid that displaced by the object [7]. Floating drug delivery systems (FDDS) is one of a methodology that has been produced so as to expand the gastric residence time of orally administered dosage form. Single and compound unit system have been fabricated [8]. Oral compound unit dosage form, for example, microspheres have gotten much consideration as altered/controlled the drug delivery from dosage form. These frameworks were more consistently dispersed in the gastrointestinal tract, subsequently bringing about a more uniform absorption and decreasing patient-to-patient variation[9]. Floating and mucoadhesive gastric-retentive delivery system was designed to retained in stomach and float for 6 and 24 hours, correspondingly. This formulation was prepared using a liquid multi-layering process to compose five layers of a hallow spherical shell, a waterproof, a drug, a release retarding film and a mucoadhesive layer[10]. A pH-responsive of bi-polymer of sodium alginate and pectin have been explored as raft-forming polymers using sodium bicarbonate and calcium carbonate as gas-generating and calcium ion sources, respectively. This study has shown the capability of bi-polymer to form strong and flexible raft[11].

Sodium carboxymethyl cellulose is soluble in hot and cold water. At low concentrations, solutions are characterized by high viscosity that makes them useful in pharmaceutical applications, such as thickening and stabilizing agent[12]. The viscosity of Na CMC solution is proportional to degree of polymerization and molecular weight (chain length). It is forming clear colloids in water and pharmaceutically employed as coating and binder in tablet, viscosity enhancing agent, water absorbing agent in wound dressing and as a disintegrant in capsule dosage forms[13]. Calcium and Magnesium carbonates are practically insoluble in water and soluble in dilute acids with liberation of CO_2 causing effervescent[14]. They have local and fast acting antacid by rapid dissolution and increasing in the gastric pH.

Materials and Methods

Materials

Calcium carbonate, Magnesium carbonates, sodium carboxy methyl cellulose grade CRT 100 PA Walocel® Dow Wolff Cellulosic (Germany) and cross carmelose sodium were used in the formulation of antacid tablets.

Preparation of tablets

Four formulas of antacid tablets were prepared using direct compression method. Table (1) shows the Formulas 1 and 2 with carbonates to sodium caboxymethyl cellulose ratio 2.25:1 and 5.5:1 respectively. The ingredients were tumbled in plastic sachet for a minute and tablet machine (Pharma Tech international - India) were set to hold 700 mg of formula to get a compressed tablet. The formulas 3 and 4 were prepared through double layer compressed tablets, ingredients in table(2) were used in the first and second layer. The carbonates to sodium caboxymethyl cellulose ratio in the first layer were 2.25:1 and 5.5:1 respectively.

Table (1): Compositions of formulas 1 and 2

Materials	Formula (1)	Formula (2)
Calcium Carbonate	400mg	490mg
Magnesium Carbonate	50mg	60mg
Sodium Carboxymethyl Cellulose	200mg	100mg
Cross Carmelose Sodium	50mg	50mg
Total weight	700mg	700mg

Table (2): Compositions of first and second layer in formulas 3 and 4

Layer	Materials	Formula (3)	Formula (4)
First	Calcium Carbonate	286mg	350mg
	Magnesium Carbonate	36mg	43.5mg
	Sodium Carboxymethyl Cellulose	143mg	71.5mg
	Cross Carmelose Sodium	35mg	35mg
Second	Calcium Carbonate	164.5mg	164.5mg
	Magnesium Carbonate	20.5mg	20.5mg
	Cross Carmelose sodium	15mg	15mg
Total weight		700mg	700mg

Evaluation of antacid tablets

The produced tablets were subjected to the physical characterization and weight variation study. The hardness and friability tests were carried out using Erweka hardness (TBH-100 Germany) and friability (TAR, Germany) testers, respectively. The content uniformity study was replaced by mass variation test according Appendix XII C of British Pharmacopoeia 2012, due to the tablet weight more than 650mg and the content of active ingredients more than 25mg[14]. The buoyancy measurement was performed using USP XXX Pharmacopeia [15] dissolution apparatus to evaluate tablet in 0.1N HCl as artificial gastric juice (AGJ). The experiment was carried out for two hours by putting of the pre weighed tablet into dissolution jar that contains 500mL of AGJ. The rotation speed of paddle was 100 rpm; the remnant of the tablet was taken off and left for 48hours inside hood to dry. The remained dried tablet was reweighed and the difference in weight was calculated. This test was carried out in triplicate for each formula.

The acid neutralization capacity was measured for each of the intact and pulverized tablets. It was measured using DL53 Titrator (Mettler Toledo – Switzerland).

A modified method of Washington and colleagues was applied in this experiment by addition of one intact tablets (or powder of one tablets) into a solution containing 30mL of 0.1N HCl and 70mL Mili-Q water. AGJ was pumped into solution at 4mL/minute and syringe pump was used to remove the reacted mixture from other side of beaker with rate that equal to addition of the AGJ [16]. This was stirred continuously using a fixed plastic tube around the shift of stirrer in order to prevent turbulence mixing of raft layer and the pH was monitored and recorded. The pH at the raft was measured by another pH probe settled into raft layer. The test was carried out at 37°C using constant temperature cabinet.

Statistical analysis

The one-way ANOVA was used to analyze the differences in the measured properties of the prepared antacid tablets.

Results and Discussion

The prepared antacid tablets were showed physical characterization as shown in Table (**3**. All formulas exhibited low weight variation that might be as a result of manual feeding of powder into die chamber of tablet machine. The mass variation test was passed by all the prepared formulas because of the means of individual weight of ten tablets were more than 98.5 and less than 101.5%.

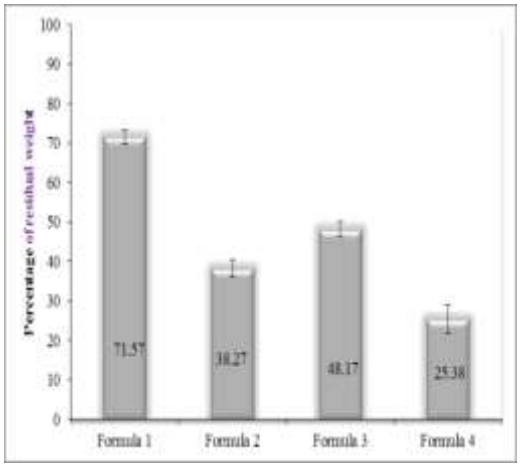
Table (3): The physical characterization of the prepared antacid tablets

Formulas	Hardness (Kg/cm^2±SD), n=10	Friability (%±SD), n=3	Weight variation (%±SD), n=10
Formula 1	7.9±0.24	0.54±0.03	99.6±0.7
Formula 2	7.85±0.2	0.6±0.04	99.3±0.75
Formula 3	8±0,25	0.58±0.03	99.8±0.56
Formula 4	7.9±0.24	0.61±0.03	99.3±0.62

Moss and colleagues showed that, the carbonate content of liquid Gaviscon® had an important role in floating of raft forming antacid [17]. Therefore, the floating tablet was manufactured by mixing of calcium and magnesium carbonates with hydrogel forming polymer, through maintaining of a low bulk density of wetted tablet by swelling on contact

with gastric fluid and trapping of the CO_2 gas that that formed upon the reaction of carbonate containing antacid with AGJ. Then as a consequence, the wetted tablet has to be buoyant. In addition, a sustained release of acid neutralizing agent was occurring within the erosion of the hydrogel upon stirring.

The degree of floating was measured using the residual weight calculations. The experiment was carried out in artificial gastric fluid so as to observe the possible differences. The obtained results showed that, floating behavior was increased as molecular weight is increased and hydration rate is decreased of the polymer. In the preparation of sustained release floating antacid tablets, two formulas were employed using different percentages of active ingredients and polymer, floatation was accomplished by incorporation of gas generating calcium and magnesium carbonates that generate CO_2 and act as active ingredient; sodium CMC was use as anionic polymer that mediate FDDS design on basis of delay gastric emptying time and buoyancy principle. All the prepared antacid tablets showed buoyancy as shown in figure(1). Besides, there was a significant difference ($p<0.05$) in buoyancies among all the prepared formulas, However, first formula showed an average of buoyancy more than the second formula (71.5 % and 38%) while the 4th formula showed the least buoyancy than others. In addition, the results reveal that the increase in the percentage of sodium CMC enhanced the buoyancy. This effect would be responsible for decline in the release of calcium and magnesium carbonates, so give a sustained release compound by acting as rate controlling excipient.



Figure(1): The effect of content and number of layers of antacid formulas 1, 2, 3 and 4 on the buoyancy, (mean ± SD, n=3).

The Cross carmelose sodium was used within 5% concentration[13] in tablet dosage form in formulas 1, 2, and in first layer of 3 and 4 while in the second layers was 7.5% in order to fasten the porosity and subsequently the swelling. Formula 1 showed the highest buoyancy that is might be due to highest percentage of anionic polymer used than rest of formulas, in addition to the lowest percentage of magnesium carbonate. The 4th formula showed the least buoyancy than others. This might be attributed to the lowest anionic polymer content and the highest amount of carbonates.

The acid neutralizing capacities of the prepared formulas were studied and the obtained results were found to be increasing with time as shown in figure(2). All formulas showed the sustained action of acid neutralization that might result from the hydrogel formation of sodium carboxy methyl cellulose upon contact with AGJ. This formation reduced the dissolution and release of antacid agents from formulas as used earlier by Abbasi and his collegues[18]. Though, formula 4 showed the highest effect with a significant difference ($p<0.05$) from the others. While formula 1 showed the lowest effect. Formulas 2 and 3 showed similar effect. The lowest effect that found in formula 1 might be a result of the low content of the salts of antacid which is in the same trend of finding of Jagadesh[19]. The highest effect of formula 4 might be achieved as result of the high content of antacid as well as the effect of the rapid release of antacid from the second compressed layer that free from sodium carboxymethyl cellulose polymer. This finding with agreement of the studies on the formulation of sustained release bi layer tablets formulation containing fast release layer[20].

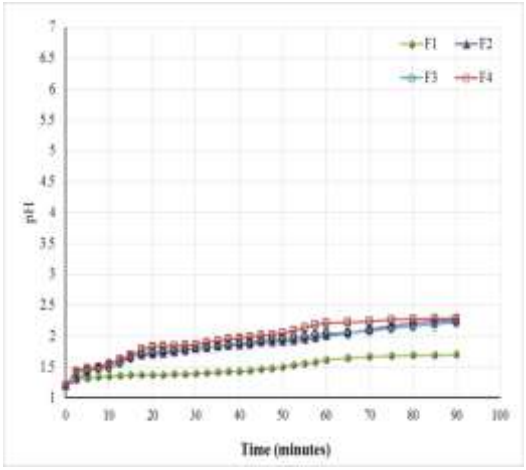


Figure (2): The effect of composition on acid neutralizing capacity of formulas 1, 2, 3 and 4; (mean ± SD, n=3).

As antacid tablets dosage form is commonly administered to be taken by chewing [21] or crushing tablet before swallowing. Therefore, formulas 3 and 4 were selected and pulverized by mortar and pestle. They were studied for acid neutralizing capacity on comparison with intact tablets and the results obtained as shown in Figure 2. The pulverized tablets of both formulas 3 and 4 showed significant ($p<0.05$) and higher acid neutralizing capacity than that in intact forms as presented in figure (3).

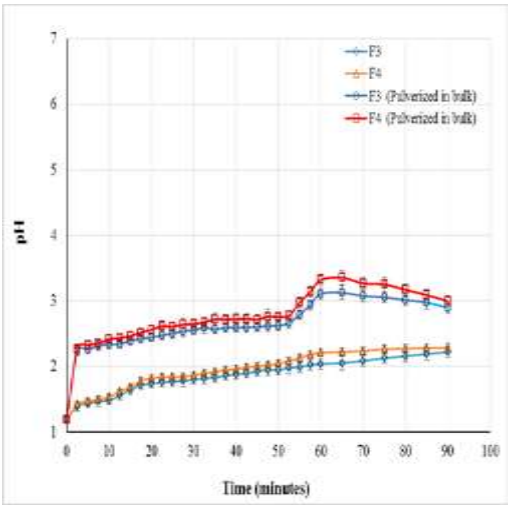


Figure (3) : The effect of pulverization on acid neutralizing capacity of formulas 3 and 4; (mean ± SD, n=3) .

In addition, boosting effect at time of 52.5 to 60 minutes was noticed. However, both pulverized formulas 3 and 4 did not show a difference in the acid neutralizing capacity in the bulk of AGJ.

Various semisynthetic polysaccharides have been studied and invented to be raft forming agents and naturals are preferred on therapeutic bases and increased the acceptance by the patients [22].

The raft was formed on the top just upon addition of pulverized tablet onto the AGJ medium for both formulas 3 and 4. The rafts were survived to end of the acid neutralizing capacity study. Figure 4 shows the acid neutralizing capacity of pulverized formulas 3 and 4 in bulk and in raft.

The raft showed significant ($p<0.05$) and higher capacity to neutralize the acid in both formulas than that in bulk. The pH's at raft and bulk were approached to equal values after an hour, that reveals the exhaustion of reservoir of acid neutralizing agents in the formulas. Conversely, the resistance persists to the end of experiment.

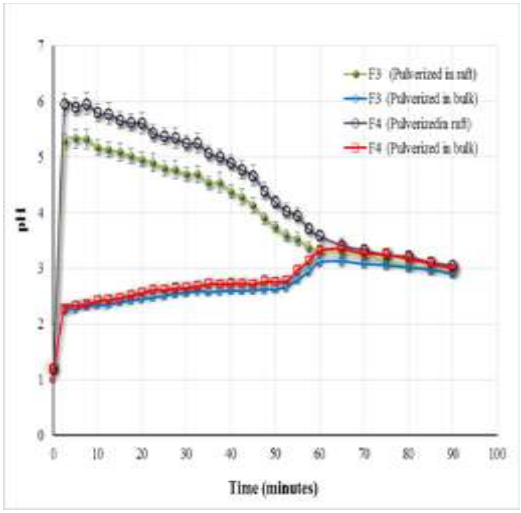


Figure (4): The acid neutralizing capacity in bulk and raft for pulverized formulas 3 and 4; (mean ± SD, n=3).

Conclusion and Future Works

According to the result obtained from this study it is concluded that a sustained release FDDS can be prepared using sodium CMC with magnesium and calcium carbonate. The buoyancy of the prepared FDDS is remarkably affected by the ratio of sodium CMC and magnesium carbonate. All formulas of mono and bilayer tablets showed the sustained action of acid neutralization and formation of raft. Besides, bilayer tablets showed a significant higher level of acid neutralizing capacity. Moreover, the pulverized tablets of formulas 3 and 4 exhibited significant higher acid neutralizing capacity in raft than that in the bulk of AGJ medium. Further works are required to test strength and physical resistance of raft texture.

References

1. Barkun A, Leontiadis G. Systematic Review of the Symptom Burden, Quality of Life Impairment and Costs Associated with Peptic Ulcer Disease. The American Journal of Medicine. 2010;123(4):358-66.e2.
2. Ching C-K, Lam S-K. Antacids. Drugs. 1994;47(2):305-17.
3. Fritsch C, Hausler F, Seedig J L, inventorsAntacid preparation having a prolonged gastric residence time. USA patent 5217794. 1993.
4. Berner B, Louie-Helm J. Tablet shapes to enhance gastric retention of swellable controlled-release oral dosage forms. Google Patents; 2002.
5. Vo AQ, Feng X, Morott JT, Pimparade MB, Tiwari RV, Zhang F, et al. A novel floating controlled release drug delivery system prepared by hot- melt extrusion. Eur J Pharm Biopharm. 2016;98:108-21.
6. Chen YC, Ho HO, Liu DZ, Siow WS, Sheu MT. Swelling/floating capability and drug release characterizations of gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose. PLoS One. 2015 ; 10 (1) :e 0116914.
7. Forsyth M. Collins English Dictionary: HarperCollins Publishers Limited; 2014.
8. Srivastava AK, Ridhurkar DN,Wadhwa S.Floating microspheres of cimetidine:formulation characterization and in vitro evaluation .Acta Pharm. 2005 ;55 (3):277-85.
9. Mazer N, Abisch E, Gfeller JC, Laplanche R, Bauerfeind P, Cucala M, et al. Intragastric behavior and absorption kinetics of a normal and "floating" modified-release capsule of isradipine under fasted and fed conditions. J Pharm Sci. 1988;77(8):647-57.
10. Zhang C, Tang J, Liu D, Li X, Cheng L, Tang X. Design and evaluation of an innovative floating and bioadhesive multiparticulate drug delivery system based on hollow structure. Int J Pharm. 2016;503(1-2):41-55.
11. Hanif M, Abbas G. pH-responsive alginate–pectin polymeric rafts and their characterization. Advances in Polymer Technology. 2017;37(1):12.
12. Vais AE, Palazoglu TK, Sandeep KP, Daubert CR. Rheological Characterization Of Carboxymethylcellulose Solution Under Aseptic Processing Conditions. Journal of Food Process Engineering. 2002;25(1):41-61.
13. Rowe RC, Quinn ME, Sheskey PJ, editors. Handbook of Pharmaceutical Excipients. 6th ed. London, UK: Pharmaceutical Press 2009.
14. Pharmacopoeia B. The British Pharmacopoeia. London Great Britain: London : Published for the General Medical Council by Constable & Co.; 2012.
15. Pharmacopeia U. United States Pharmacopeia and National Formulary (USP 30-NF 25) [CDROM]. Rockville M, editor2007.
16. Washington N, Wilson CG, Davis SS. Evaluation of ' raft-forming' antacid neutralizing capacity: in vitro and in vivo correlations. International Journal of Pharmaceutics. 1985;27:279-86.
17. Moss HA, Washington N, Greaves JL. Anti-reflux agents: stratification or floatation? European Journal of Castroenterology & Hepatology. 1990;245:51.
18. Abbasi S, Yousefi G, Ansari AA, Mohammadi-Samani S. Formulation and in vitro evaluation of a fast-disintegrating/sustained dual release bucoadhesive bilayer tablet of captopril for treatment of hypertension crises. Research in Pharmaceutical Sciences. 2016;11(4):274-83.
19. Jagadesh DK, K N DCN. Study of Acid Neutralizing Capacity of Various Antacid Formulations2015.
20. Shiyani B, Gattani S, Surana S. Formulation and Evaluation of Bi-layer Tablet of Metoclopramide Hydrochloride and Ibuprofen. AAPS PharmSciTech. 2008;9(3):818-27.
21. British Medical A. British National Formulary 67. Standard ed. ed: The British Medical Association and The Pharmaceutical Society of Great Britain; 2014.
22. Kapadia CJ, Mane VB. Raft-Forming Agents: Antireflux Formulations. Drug Development and Industrial Phar Macy . 2007;33(12):1350-61.