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Research Article

New Natural Marine Antacid Drug from Cuttlebone

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ABSTRACT

Background: Antacids are the most commonly used medications for fast symptomatic relief of gastric disorders. Because of adverse effects, low efficiency and the high cost of some chemical antacids, identifying a natural medicine with high efficiency and low cost seems useful. Therefore, the aim of the present study was to prepare antacid tablets from Cuttlefish bone and assessment of its antacid properties.
Methods: 24 different formulations of cuttlefish bone were prepared by direct compression using different fillers (starch, cellulose, lactose, and mixture of those) in different ratios of the drug. Characterization of powders and tablets was done on all formulations and marketed dosage forms (calcium carbonate and Al-Mg).
Results: Weight uniformity, hardness, and friability of all formulations were in acceptable range. Tablets prepared by calcined cuttlebone disintegrated in longer time due to their higher hardness which were mostly higher than 5 Kg. Also, disintegration time of formulations 50-50 (lower dose of cuttlebone) was less than other tablets (2 minutes or less). Results of antacid capacity showed that formulations 90-10 and 80-20 raise the acidic pH of the medium above 7.5, which were the same as or more than the capacity of the marketed tablets.
Conclusion: Tablets were prepared by 90 or 80% of either calcined or non-calcined cuttlebone showed the highest antacid capacity.

Introduction

Sepia pharaonis is one of the invertebrates of the Persian Gulf in the south of Iran (Figure 1). In the back part of the Sepia (cuttlefish), there is an oval shape and spongy bone named cuttlebone (CB) which is called seabed in native dialect (Figure 2). CB is composed of two parts: organic part (Protein and β-Chitin), and inorganic part (calcium carbonate and calcium phosphate) with lots of pores. So CB is formed mainly of calcium carbonate and Chitin.[1-3] CB has many pharmaceutical and industrial applications e.g. it is used in the treatment of bleeding and external infections. It is added to birdseed for adjusting the function of liver and kidney and digestion system.[4] Improvements have been achieved in the removal of dyes and toxic elements from water and wastes using CB as an adsorbent.[5] One of another its application is using its antacid property. Generally, antacid drugs can neutralize the acid in the gastric juice and increase pH.

Figure 1. Picture of Sepia pharaonis.

Figure 2. Picture of Cuttlebone (CB).

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They can apply for treatment of gastritis, peptic ulcer, and gastric reflux diseases.[6] The most popular antacid drugs are calcium carbonate and aluminium-magnesium tablets. However, natural compounds such as natural dietary fibre,[7] herbal extracts,[6] natural clinoptilolite[8] and medicinal plants, spices, vegetables and crude drugs[9,10] have been used as antacid drugs. Since the CB is a natural material with a high percent of $CaCO_3$, it can be used and formulated by different fillers as a marine natural antacid drug.

Materials and Methods

Preparation of crude CB powder

Cuttlebone was gathered from Bushehr coast, then was washed and dried in free air in order to lose its smell. After drying, the clean cuttlebone was powdered and completely mixed to 60-100 mesh size.

Preparation of calcined CB powder

Crude CB powder was heated in a furnace at 800 °C for 2 hours, then washed with water several times and dried in an oven at 80 °C for 24 hours. Again, the obtained powder was washed and dried in an oven at 100°C for 12 hours and heated in a furnace at 400 °C for 4 hours until calcination was completed. From 10g of crude CB powder about 5g of calcined CB powder was obtained.

Characterization

Analysis of elements and compounds of CB were characterized by means of CHN, XRF, XRD and FTIR techniques. CHN studies were performed using a COSTECH ECS 4010 apparatus and XRF studies were conducted using a PHILIPS PW1480 instrument. XRD studies were performed using PHILIPS X/PERTPRO and FTIR by Bruker VERTX70.[2,11] Back titration method with NaOH 0.1 M was used to measure the amount of carbonate of CB. To do this CB was dissolved in excess and a certain amount of HCl and was heated for the evolution of CO_2 gas for 5 min, and then an excess amount of HCl was titrated with NaOH.

Formulation of drugs

The mixtures of crude CB powder and different fillers such as cellulose, lactose, and starch with the different composition of CB: filler in ratios of 50:50, 60:40, 80:20 and 90:10 were prepared (Table 1). The tablets were prepared by direct compression method (Erweka AR402) and characterized for powder flowability, friability, weight uniformity, hardness, disintegration time and antacid capacity according to USP. Marketed dosage forms (calcium carbonate and Al-Mg) were characterized as well.

Flowability of CB Powder

Flowability of CB Powder with fillers was measured by flow meter apparatus in g/sec. For all of the formulations, the corresponding powders were poured into the funnel of apparatus and flowability of powders was calculated by apparatus.

Table 1. Components of tablets formulations in percentage.

Components of formulations		
CB (%)	**Filler (%)**	**Magnesium stearate (%)**
crude (90)	avicel (9)	1
crude (80)	avicel (19)	1
crude (60)	avicel (39)	1
crude (50)	avicel (49)	1
crude (90)	starch (9)	1
crude (80)	starch (19)	1
crude (60)	starch (39)	1
crude (50)	starch (49)	1
crude (90)	Lactose(9)	1
crude (80)	lactose(19)	1
crude (60)	lactose (39)	1
crude (50)	lactose (49)	1
calcined(90)	avicel(9)	1
calcined (80)	avicel(19)	1
calcined(90)	starch(9)	1
calcined(80)	starch (19)	1
calcined(90)	lactose(9)	1
calcined(80)	lactose(19)	1
crude (90)	avicel-lactose(9) *	1
crude(90)	avicel-starch (9) *	1
crude(90)	avicel-starch (9) *	1
calcined(90)	avicel- lactose(9) *	1
calcined(90)	avicel-starch(9) *	1
calcined(90)	starch-lactose (9) *	1

*ratio of fillers is 1:1.

Friability test

Friability tests were evaluated with friability apparatus for 20 weighted tablets of formulated drugs, rounded at 25 rpm for 4 minutes. Friability percent was calculated via the following formula:

$$\text{Friability (\%)} = \frac{W1-W2}{W1} \times 100 \qquad \text{Eq. (1)}$$

None of the tablets should be broken or capped. Friability percent should be less from 0.5-1 %.

Weight uniformity

20 tablets were selected randomly from each formulation and weighted by digital balance.

Hardness Test

The hardness of formulated drugs was measured by hardness apparatus in Kg. In this method, 10 tablets were selected randomly from each formulated drugs and hardness of them were determined by apparatus. The favorite hardness should be obtained between 4-6 Kg.

Disintegration Test

Disintegration time for each formulated drugs was measured by related apparatus in distilled water. For this purpose, 6 tablets from each formulated drugs were selected and placed into the tubes of the apparatus in water bath 37°C with regular movements. The disintegration time of the first and last tablets was determined.

Antacid capacity

The antacid capacity of formulated drugs was evaluated in the presence of synthetic gastric juice (SGJ), (HCl, then 200mL, pH 1.5 and NaCl 0.3 g) with two methods. 500-

600 mg of drug (one tablet) with an aliquot of 200 mL of SGJ was mixed at 37°C and stirred at 100 rpm. After one hour, the solution was filtered and 25 mL of the solution was titrated with NaOH 0.1 M and then pH of media was calculated. In another method, 500-600 mg of the drug with an aliquot of 200 mL of SGJ was stirred at 37°C at 100 rpm on heater stirrer, pH of media was measured in different intervals by pH meter.

Results

Elemental and chemical analysis of Crude CB

Amount of carbonate by back titration was obtained through a triplex experiment, 93.25%, 90.5% and 92.5%. The average of them was 92.08%. CHN analysis of CB is shown in Figure 3 and Table 2. CHN analysis of CB showed the amount of C 12.45%, N 0.36%, and H 1.49%. The amount of C was more than two other elements (Figure 3) because CB is composed mainly of $CaCO_3$ that 12.45% of C comparable to 12% of C in $CaCO_3$. According to the average of measured $CaCO_3$ that was obtained 92.08%, 1.74 mg out of 1.89 mg of CB is $CaCO_3$ and 12% of $CaCO_3$ is carbon (0.2088 mg). This amount is well comparable to 0.235 mg C or 12.45% C in Table 1.The more amount of C is related to C of chitin and chitosan of CB.XRF analysis of CB showed the existence of the following elements such as Na, Mg, K, Si, S, P, Cl and especially Ca. XRF analysis of CB showed 44.71% CaO (or 31.93% Ca). In comparison to the average of carbonate based on Ca (92.08%) that measured in CB (or 36.83% Ca), so the amount of Ca is well determined (Table 3). XRD spectrum of CB confirmed the presence of CaCO3 (Figure 4). The peak at 3426 cm^{-1} of FTIR is related to OH and NH_2 bonds in chitin. Peaks at 1465, 865 and 708 cm^{-1} are attributed to C-O bond in carbonate ion. Absorptions at 2521 cm^{-1} and 2923 cm^{-1} are related to HCO_3^- ion and C-H bonds, respectively (Figure 5).

Formulation of drugs

Tablets were prepared from crude or calcined CB, different fillers with different proportions (starch, lactose, avicel and mixture of fillers) and magnesium stearate as a lubricant (Table 1). All the components were mixed completely and the tablets were prepared by direct compression method. Flowability of CB powder with fillers was shown in Table 4. Formulations of 80:20 and 90:10 of crude and calcined CB with the fillers of starch and avicel and, formulation of 80:20 calcined and 90:10 calcined with lactose had a maximum of flowability. Generally, formulations of 50:50 of drug-filler had minimum flowability. With the mixture of fillers, formulation of calcined 90:10 and crude 90:10 with the mixtures of avicel- starch had a maximum of flowability.

Table 2. CHN analysis of crude CB.

	Retention Time [min]	Response	Weight [mg]	Weight[%]	Peak Type	Element Name
1	0.983	10.732	0.007	0.36	Refer	Nitrogen
3	2.017	1398.087	0.235	12.45	Refer	Carbon
5	6.897	126.149	0.028	1.49	Refer	Hydrogen
	Total		1.890	14.30		

Table 3. XRF analysis of crude CB.

SiO_2 (%)	Al_2O_3 (%)	Fe_2O_3 (%)	CaO (%)	Na_2O (%)	K_2O (%)	MgO (%)
0.12	0.04	0.03	44.71	2.25	0.07	0.36
TiO_2 (%)	**MnO (%)**	**P_2O_5 (%)**	**SO_3 (%)**	**L.O.I[a] (%)**	**Cl (ppm)**	**Sr (ppm)**
0.012	0.006	0.102	0.255	53.96	24500	1756

[a] Loss on ignition

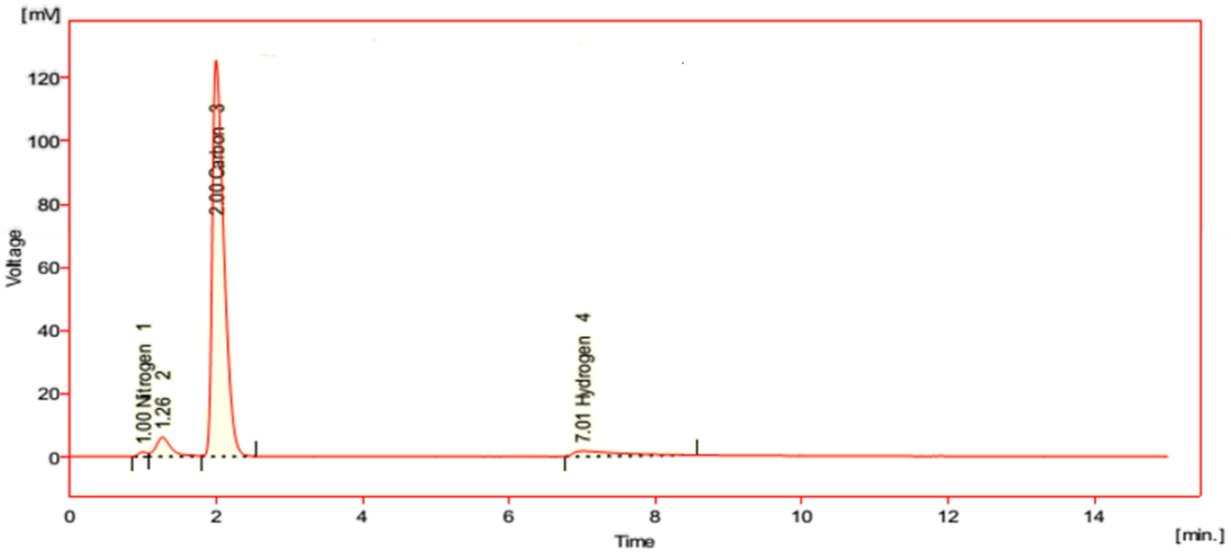

Figure 3. CHN analysis of crude CB. C 12.45%, N 0.36% and H 1.49%.

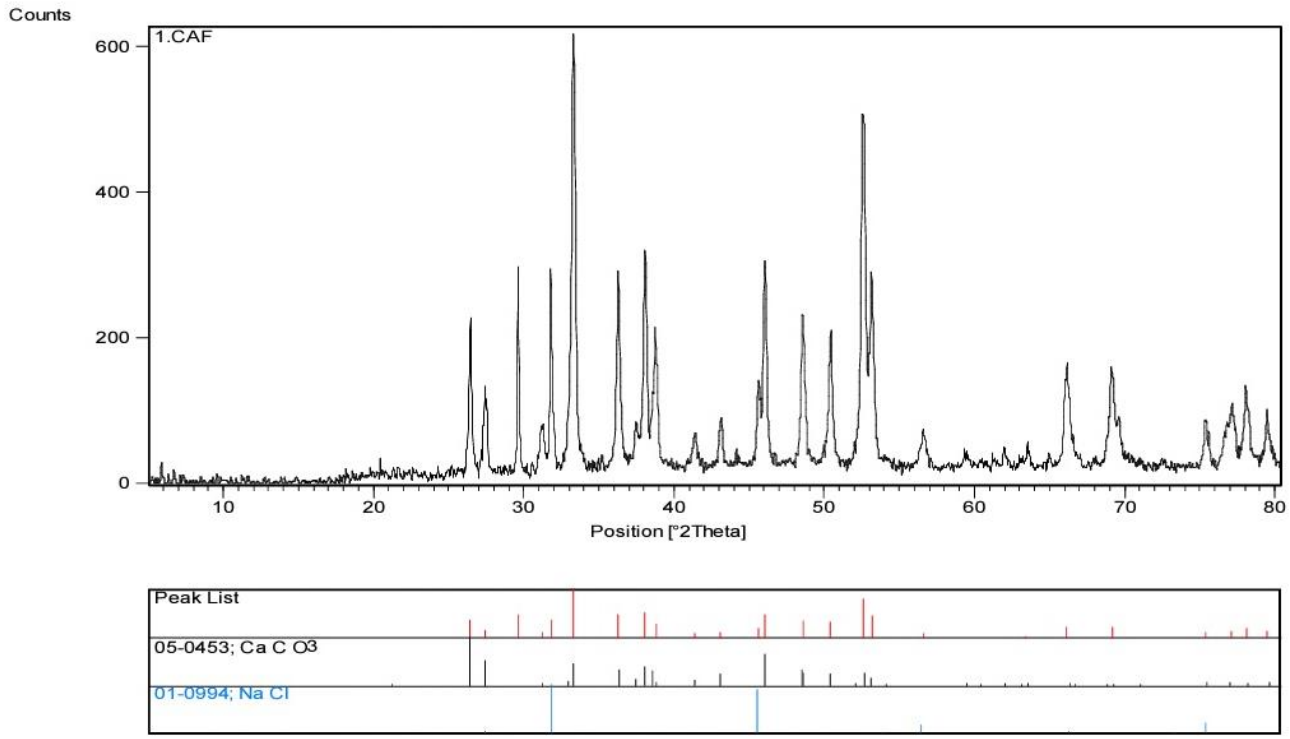

Figure 4 XRD spectrum of CB powder.

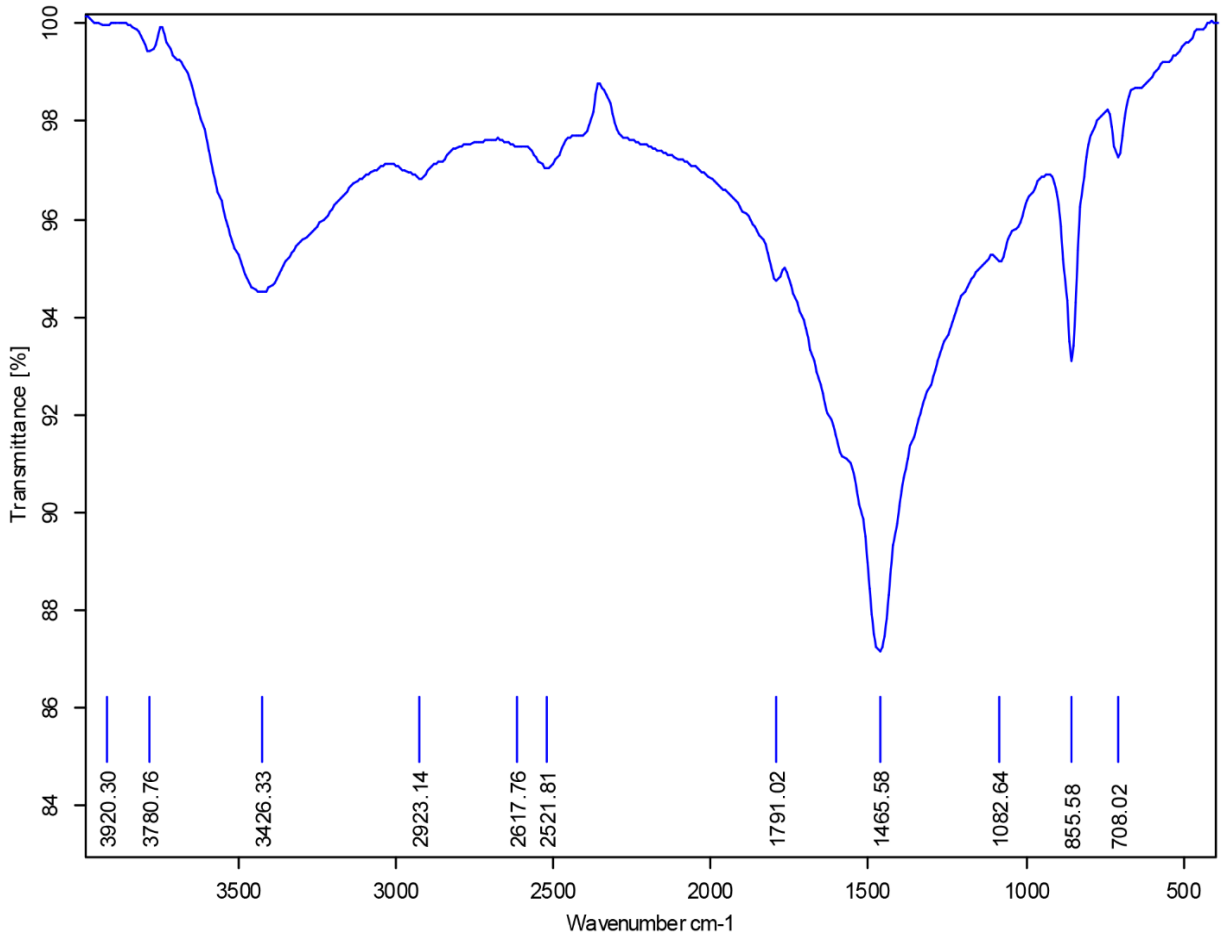

Figure 5. FTIR spectrum of CB.

Table 4. Flowability and weight uniformity of drug-filler with different formulations.

The proportion of drug to filler	Type of filler					
	Avicel		Starch		Lactose	
	Flowability (g/sec)	Weight uniformity (g)	Flowability (g/sec)	Weight uniformity (g)	Flowability (g/sec)	Weight uniformity (g)
CrudeCB- 50:50	10.4	0.587±0.002	9	0.589±0.002	10.7	0.589±0.002
CrudeCB-60:40	11.1	0.579±0.002	11.2	0.589±0.003	13.8	0.589±0.002
CrudeCB-80:20	13.8	0.588±0.002	13.8	0.589±0.002	14.5	0.589±0.002
CrudeCB- 90:10	14.3	0.589±0.002	14.7	0.589±0.002	12.8	0.589±0.002
CalcinedCB-80:20	14.9	0.590±0.002	16	0.589±0.013	17	0.589±0.002
CalcinedCB-90:10	14.5	0.588±0.002	14.9	0.590±0.002	15.6	0.589±0.002

Table 5. Physicochemical properties of marketed drugs.

Physicochemical properties	Marketed drug	
	Al-Mg	$CaCO_3$
Weight uniformity(in g)	0.553± 0.014	1.352± 0.008
friability (in percent)	0%	0%
Disintegration time(first and last tablet in minute)	3.5-5.5	3-6
Hardness(in Kg)	9.37±0.11	9.91±0.16
pH(titration method) after 20 min.	5.20	5.42
pH(Determination by pHmeter) after 120 min.	7.27	7.5

Table 6. Some physicochemical properties of drug: mixture of fillers.

The proportion of drug to the mixture of fillers* 90:10	Physicochemical property				
	Weight uniformity (g)	Friability (percent)	Disintegration time(first and last tablet in minute)	Hardness(Kg)	Flow ability of powder (g/sec)
Crude CB: Avicel-Starch	0.589±0.002	0.00	3.5, 4.5	6.86±0.30	16
Crude CB: Avicel-Lactose	0.589±0.002	0.34	2, 3.5	5.49±0.27	15.5
Crude CB: Starch-Lactose	0.589±0.002	0.08	3, 3.5	6.47±0.24	14.5
Calcined CB: Avicel-Starch	0.589±0.002	0.42	3, 5	5.70±0.31	15.5
Calcined CB: Avicel-Lactose	0.589±0.002	0.00	4, 4.5	6.57±0.34	14
Calcined CB: Starch-Lactose	0.589±0.002	0.42	2.5, 3.5	5.50±0.28	13.8

*ratio of the mixture of fillers is 1:1.

Average of the weight of tablets with different fillers and marketed dosage forms (calcium carbonate and Al-Mg tablets) were shown in Tables 4, 5 and 6. The weight of all of the tablets was in the range of 0.577- 0.592 g with allowed percentage error (5%).

Friability percent of tablets from CB and different fillers were shown in Tables 6 and 7. Friability percent of all of the tablets were less than 1 % except formulation of 50-50 with starch as filler. Minimum of friability percent in the formulation of 90-10 and 80-20 and maximum of friability percent was obtained in the formulation of 50-50. Hardness test also showed us similar results. The hardness of formulated tablets from CB and marketed dosage tablets were shown in Tables 5, 6 and 7. The hardness of all of the prepared tablets was in the range of 4-6 Kg except formulation of 50-50.

Disintegration test of all of the tablets with different fillers and marketed dosage were shown in Tables 5, 6 and 8. Minimum disintegration time with avicel as filler for the formulation of calcined 90-10 and maximum disintegration time for the formulation of crude 60-40 were obtained. Minimum disintegration time with starch as filler for the formulation of crude 80-20 and maximum disintegration time for formulations of crude 60-40 and calcined 90-10 was obtained. Minimum disintegration time with lactose as filler for the formulation of crude 50-50 and maximum disintegration time for formulations of crude 90-10 and calcined 80-20 was obtained.Generally, disintegration time for all of the tablets prepared with the mixture of fillers, have been increased. For example, the disintegration time of the final tablet for formulation calcined 90-10 with avicel-starch (1:1) was 5 minute, whereas with avicel alone was1.5 minute. Also, among the tablets with the mixture of fillers, the disintegration time of the formulation of calcined 90-10with avicel-starch (1:1) was similar or near to disintegration time of the marketed dosage.

Table 7. Friability and hardness of drug: filler in different formulations.

The proportion of drug to filler	Type of filler					
	Lactose		Starch		Avicel	
	Hardness(in Kg)	Friability percent	Hardness(in Kg)	Friability percent	Hardness(in Kg)	Friability percent
CrudeCB- 50:50	3.59±0.35	0.76	2.83±0.21	1.81	3.99±0.34	0.95
CrudeCB-60:40	4.00±0.24	0.59	6.6±0.44	0.00	6.10±0.31	0.95
crudeCB-80:20	4.97±0.30	0.51	5.01±0.28	0.51	5.40±0.46	0.34
CrudeCB- 90:10	5.58±0.24	0.34	5.46±0.30	0.34	6.07±0.37	0.42
CalcinedCB-80:20	6.00±0.27	0.25	5.83±0.33	0.35	5.91±0.26	0.00
CalcinedCB-90:10	4.96±0.27	0.51	6.43±0.31	0.00	5.65±0.27	0.42

Table 8. Disintegration time (min) of first and last tablets.

The proportion of drug to filler	Type of filler		
	Lactose	Starch	Avicel
CrudeCB- 50:50	0.67, 2	0.83, 2	1.5, 2
CrudeCB-60:40	1, 2.5	3, 5	2.5, 4
CrudeCB-80:20	1.5, 3	1, 1.5	1.5, 3
CrudeCB- 90:10	2, 4	1.9, 2.5	2, 3.5
CalcinedCB-80:20	2.5, 4	2, 4	2, 2.5
CalcinedCB-90:10	1.5, 3	2.5, 5	1.5, 1.5

The antacid capacity of tablets with different formulations and marketed dosage were shown with two methods in Tables 5, 9 – 12.

Table 9. Determination of pH by method 1 (titration, after 20 min).

The proportion of drug to filler	Type of filler		
	Lactose	Starch	Avicel
Crude CB- 50:50	1.69	1.82	1.86
Crude CB-60:40	1.77	2.48	3.3
Crude CB-80:20	3.65	4.89	2.39
Crude CB- 90:10	2.98	4.1	4.84
CalcinedCB-80:20	4.18	3.39	5.5
CalcinedCB-90:10	3.42	2.46	5

Table 10. Determination of pH by method 1 (titration, after 20 min).

The proportion of drug to filler	Type of fillers*		
	Lactose -avicel	Starch -lactose	Avicel -Starch
Crude CB- 90:10	4.94	4.41	3.45
CalcinedCB-90:10	3.42	2.42	3.50

*ratio of fillers is 1:1.

In method 1, pH of the medium after reaction of the drug with SGJ were determined using titration with NaOH 0.1 M, and maximum pH were obtained with formulations of calcined 90-10, 80-20 and crude 90-10 with avicel , crude 80-20 with starch, calcined 80-20 with lactose. Minimum of pH were obtained with crude 50-50 with three types of fillers. Regarding tablets prepared with the mixture of fillers, maximum of pH was related to crude90-10 with avicel-lactose (1:1) formulation and a minimum of pH was related to calcined 90-10 with lactose-starch (1:1) formulation. pH of the two marketed dosage were 5.20 and 5.42. Determination of acidity by pH meter apparatus (Method 2) was also done, pH of the medium after reaction of the drug with SGJ after 120 minutes are shown in Tables 11 and 12. As a whole, the maximum increase of pH in the calcined formulation and the minimum increase of pH in crude 50-50 formulations were obtained.

Discussion

One of the most prevalent gastrointestinal disorders[12-14] is peptic ulcer disease. One of the reasons is the increase of secretion of acid stomach. Current drug therapy[15-17] is neutralizing or decreasing the amount of acid. Antacids can relieve pain by neutralizing the acid of stomach.[18,19] The main components of antacids are magnesium hydroxide, aluminium hydroxide, sodium bicarbonate and calcium carbonate.

Nowadays, side effects, drug interaction and other problems of chemical drugs are caused to increase the use of natural or herbal drugs in the treatment of disease. Moreover, one of the important considerations is the cost and expense. In many studies, natural plants or marine materials are used for preparing formulations. In some of these studies, natural material is the main ingredients and in some cases, it is used as an excipient. Most related studies has been discussed following. Tavakoli et al. investigated the possibility of using Fenugreek mucilage in three different model drugs by different solubility and they concluded that Fenugreek seed mucilage can be used as a tablet binder and produces tablets with good physicochemical characteristics. The binder sustains the dissolution rate of water-soluble drug because of its hydrophilic nature.[20] In another study Mylangam et al. studied the applicability of badem gum obtained from *Terminalia catappa* Linn. as a buccoadhesive polymer using metoprolol as a model drug and they found that this natural substance has a good performance without any signs of irritation at the buccal tissue.[21]

Table 11. Determination of pH by method 2 (pH meter, after 120 min).

The proportion of drug to filler	Type of filler														
	Lactose Time(min)					Starch Time(min)					Avicel Time(min)				
	5	30	60	90	120	5	30	60	90	120	5	30	60	90	120
Crude CB-50:50	3.9	3.2	2	1.78	1.6	3.57	2.3	1.98	1.95	1.72	3.38	2.3	2.09	1.92	1.4
Crude CB-60:40	5	3.8	2.48	2	1.8	5.35	3.35	3	2.69	2.04	6.5	5.9	5.35	4.14	2.6
Crude CB-80:20	7.5	7	6.6	4.4	2.6	7.14	6.85	6	5.2	2.8	7.8	6.85	5.89	2.68	1.7
Crude CB-90:10	7.85	5.8	4.45	3.2	1.75	7.45	6.32	5.65	5	2.3	7.5	7	6.3	5.1	2
Calcined CB-80:20	9	8.2	7.32	5.8	2.8	9.05	8.1	6.41	3.9	2.7	9	7.3	7.6	5.75	2.98
Calcined CB-90:10	10.4	9.4	8.3	5.3	1.65	9.48	8.2	5.7	2.85	1.5	9.68	8.1	6.15	5.4	1.99

Table 12. Determination of pH by method 2 (pH meter, after 120 min).

The proportion of drug to the mixture of fillers*	Type of fillers														
	Lactose-Starch Time(min)					Avicel-Starch Time(min)					Avicel-Lactose Time(min)				
	120	90	60	30	5	120	90	60	30	5	120	90	60	30	5
Crude CB-90:10	7.68	6.4	5.78	4.78	2.2	7.69	6.38	5.48	4.7	2	7.75	6.7	6.3	5.1	2
Calcined CB-90:10	9.56	7.80	5.5	2.8	1.85	8.42	7.39	5.9	4.94	1.65	9	7.75	5.68	3.65	1.75

* Ratio of the mixture of fillers is 1:1.

Also Ali et al. developed a poly-herbal formulation named Habb-e-Banafsha Qawi which could be useful in cough and coryza.[22] A new wound healing agent using marine biomaterials (squid ink polysaccharide) and chitosan as a carrier and $CaCl_2$ to initiate coagulation also prepared by Huang et al. and they concluded that this system provides rapid hemostasis and protects from wound infection.[23]

One of the natural marine compounds that has antacid property is cuttlebone (CB) that contains a large amount of $CaCO_3$. In this research, we tried to prepare and introduce a new natural marine antacid drug from CB and different fillers such as starch, avicel and lactose with different formulations. CB was used in two forms, crude CB and calcined CB. In calcined form, the organic materials are eliminated by heating in an oven at 800 ℃. Different formulations are prepared from crude CB and calcined CB with fillers and mixture of fillers. In all of the formulations, the proportion of the mixture of fillers was 1:1 and magnesium stearate was used as a lubricant. Physicochemical properties of the powder and the prepared tablets such as flow ability, friability, Hardness, disintegration time and antacid capacity were determined and compared with two marketed dosage, calcium carbonate and Al-Mg tablets.

The physicochemical and antacid properties of marketed tablets are listed in Table 5. In weight uniformity test, all of the prepared tablets with different formulations had very low percentage errors that are indicated the tablets were prepared with good precision comparable to the marketed tablets. Determination of hardness test showed that the results were less than marketed tablets. Friability tests of calcined CB-starch 90-10, calcined CB- avicel: lactose 90-10 and crude CB-avicel: starch 90-10, crude CB- starch and calcined CB- avicel 80-20 formulations were completely similar to the marketed tablets. The disintegration time of crude CB-starch 60:40 and calcined CB-starch 90:10 were similar to that of the marketed ones. Because of better results of 90-10 (drug-filler) formulation with one filler, the related tests with the mixture of fillers (the proportion of mixture of fillers was used 1:1) only accomplished with 90-10 formulation.

In the determination of antacid capacity, with titration method after 20 min, crude CB-avicel 90-10, calcined CB-avicel 90-10, calcined CB-avicel 80-20, crude CB-avicel: lactose 90-10 and crude CB-starch 80-20 formulations increased the pH medium to about 5 that were comparable to marketed tablets. Generally, crude CB 90-10 and calcined CB 90-10 formulations with three type of fillers and mixture of fillers increased the pH of medium higher than 7(7.14-10.4) after 120 min that was more than related pH of the marketed tablets (7.27, 7.5). So, the experiments indicated that CB has the high antacid capacity comparable with $CaCO_3$ and Al-Mg tablets. Also, calcined CB showed the better results that could be related to the elimination of organic compounds and higher purity of it.

Conclusion

All of the prepared formulations from CB, especially formulations with proportions of 90-10 and 80-20 (drug-filler), showed the appropriate and acceptable physicochemical properties and very good antacid capacity. Then, we can use it as a good natural marine antacid drug that has less side effects, good efficiency, inexpensive and comparable with the marketed tablets and other antacid compounds.[7,10,24]

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Conflict of Interests

The authors claim that there is no conflict of interest.

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