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Taste Masked of Eplerenone Using Egg box Method

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ORIGINAL STUDY

Taste Masked of Eplerenone Using Egg Box Method

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Abstract

Eplerenone is a selective mineralocorticoid receptor antagonist employed to manage hypertension, central serous retinopathy, and chronic heart failure. It has a highly bitter taste, which reduces patient compliance with the drug.

The aim of this study was masking the very bitter taste of the eplerenone to improve patient compliance especially for geriatric patient.

The medication was encapsulated utilizing the ionic gelation process, in which a 1% w/w sodium alginate solution was utilized to form egg box structures. Two different concentrations of $CaCl_2$ (0.5.1%w/v) were used as cross-linkers, and different drug: polymer ratios were tested. The formulas were evaluated based on their physical appearance, percentage yield, percentage drug loading, and in-vitro taste masking. The optimum formula (F4) was selected and characterized using Fourier-transform infrared spectroscopy (FTIR), Scanning Electron Microscopy (SEM) and Energy Dispersive Spectroscopy (EDS).

Finally, this study suggests that the ionic gelation approach effectively masks the intense bitterness by lowering the drug's release through the mouth pH 6.8 within 1 min. The optimum formula, F4, reduced eplerenone release to 3.2% as compared to pure eplerenone (57%), under similar conditions.

Keywords: Eplerenone, Taste masking, Egg box, Sodium alginate and cross linker

1. Introduction

Eplerenone (EPR) is a selective mineralocorticoid receptor antagonist. It is an analogue of a widely used diuretic spironolactone, exhibiting greater selectivity for mineralocorticoid receptors and higher affinity. The EPR is indicated for the treatment of hypertension, central serous retinopathy, and chronic heart failure, either as a monotherapy or in conjunction with other antihypertensive agents [1]. The molecular structure of EPR is represented as the compound 9,11a-Epoxy-7a-(methoxycarbonyl)-3-oxo-17a-pregn-4-ene-21,17-carbolactone, as depicted in (Fig. 1). The compound possesses an empirical formula of $[C_{24}H_{30}O_6]$ and a molecular weight of 414.50 gm/mol. It's a solid that displays white to off-white in color and lacks any discernible odor. The compound exhibits a solubility of less than 1 mg/mL in water, which denotes a low level of solubility (very slightly soluble). It has free solubility in acetonitrile, sparingly soluble in methanol, and very slightly soluble in ethanol. Additionally, it has a distinctly harsh flavor [2].

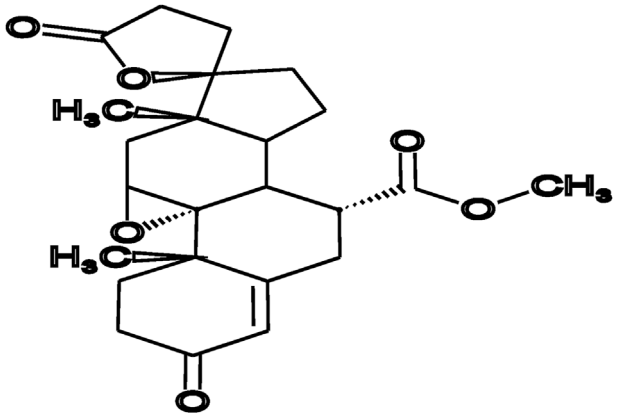

Fig. 1. Structure of EPR.

The egg-box is formed through an ionic chemical reaction called external ionic gelation. This reaction occurs between polysaccharide polymers, for instance sodium alginate (Na^+-alg), with a divalent

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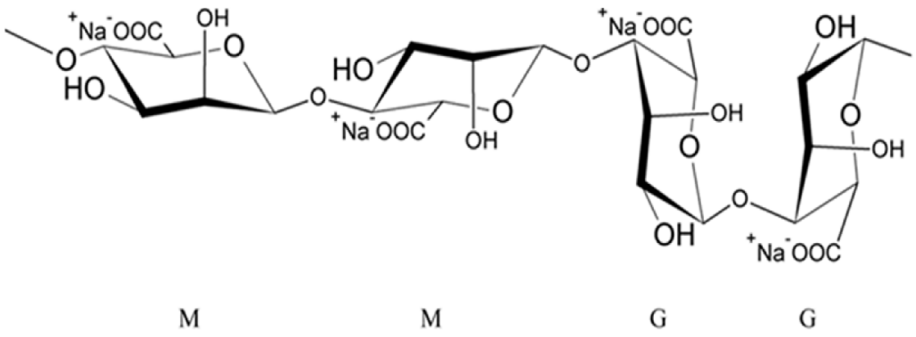

Fig. 2. Structure of sod. Alginate [3].

ion, such as calcium [3]. The goal of this reaction is to create a gel by crosslinking the polymers. This gel has the ability to encapsulate medicine within it, resulting in a prolonged release of the drug. It also effectively masks the unpleasant taste of certain drugs and offers other benefits [4].

This study attempted to reduce the bitter taste of EPR by employing Egg-box encapsulation to contain the drug. This resulted in a reduction of medicine release in the oral cavity (phosphate buffer saline pH 6.8) within 1 min. The experiment involved varying ratios of drug to sodium alginate (Fig. 2) and two different concentrations of $CaCl_2$ as a crosslinker (Fig. 3) [3].

2. Material

Eplerenone was purchased from Zhejiang Shenzhou pharmaceutical Co., LTD, China. Sodium alginate was provided by Thomas Baker, India, Calcium chloride was purchased from MERCK pharmaceutical Co., LTD. Germany. Disodium hydrogen phosphate (Na_2HPO_4), and Potassium dihydrogen phosphate (KH_2PO_4), was provided by Thomas Baker, India.

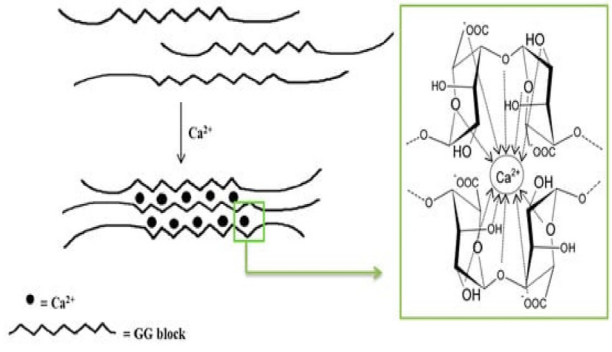

Fig. 3. Alginate gel formation by calcium cations ("egg–box" model) [3].

3. Method

The hydrogel of sodium alginate (1% w/v) was produced and then dispersed in the external phase ratio (EPR) at various concentrations, as indicated in Table 1. The dispersion was achieved by gradually adding the hydrogel to the EPR while continuously stirring with a magnetic stirrer at 400 rpm and 30 °C for 30 min. Subsequently, the mixture was dropped into a solution of $CaCl_2$ (w/v) with different concentrations, which served as a crosslinker. This was done using a disposable syringe (23 gauge) to form an egg box structure (EPR-egg box). The EPR-egg box was then filtered and carefully washed with a known volume of deionized water (DW). Finally, it was placed on filter paper and dried at room temperature for 24 h (Fig. 4a–d) [3,4].

3.1. Characterization and evaluation

3.1.1. Physical appearance

After formulating the EPR-egg box solutions, the impact of varying concentrations of $CaCl_2$ was investigated on the shape of the egg box.

3.1.2. Percentage yield

To get the yield percentage, weigh the amount of weight of the dried EPR-egg box and then calculate it using the equation shown below [6,7].

Table 1. Formulation of EPR-egg box.

Formula code	*Na^+-alg. % (w/v)	*Na^+-alg: EPL.	*EPR. (mg)	*DW (ml)	*% $CaCl_2$ (w/v)
F1	1% (200 mg)	8:1	25	20	0.5
F2	1% (200 mg)	8:1	25	20	1
F3	1% (200 mg)	8:2	50	20	1
F4	1% (200 mg)	8:3	75	20	1

*EPR: Eplerenon, Na-alg.: sodium alginate, DW:deionized water, $CaCl_2$:calicium chloride.

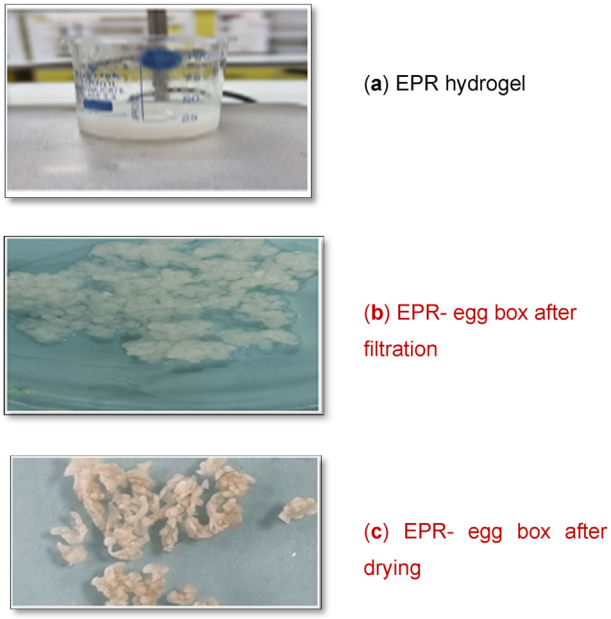

Fig. 4. Method of preparation of EPR-egg box.

$$Yield\% = \frac{weightofdriedElp.eggbox}{weightofsodiumalginat \wedge Elp.} * 100$$

3.1.3. Percentage drug loading

The drug quantity was determined in the $CaCl_2$ solution and washing water using UV spectroscopy at a wavelength of 245 nm. Subsequently, the drug loading was calculated based on the substrate weight using the equation provided below [8,9].

$$Drugloading\% = \frac{practicalweightofElp.}{TheoriticalweightofElp.} * 100$$

3.1.4. In-vitro taste masking test

Added a precise quantity of EPR-egg box (equivalent to 7.5 mg) from the prepared formula into 10 ml of phosphate buffer saline with a pH of 6.8, at a temperature of 37° Celsius. The mixture was gently shaken by hand for 60 s. Afterward, filtration via 0.45 μm filter syringe. The amount of the drug released after 60 s was measured utilizing UV spectroscopy at a wavelength of 245 nm, the percentage of drug released within 1 min, was calculated compared to pure EPR [1,5].

3.1.5. Selection of the optimum formula

Selection of the optimum formula is depended on the taste mask to be further evaluated and characterized.

3.1.6. Fourier-transform infrared spectroscopy (FTIR) study

Fourier-transform infrared spectroscopy (FTIR) by (FTIR-8300 Shimadzu, Japan) was used to detect any interaction between drugs and polymer, by placing the sample with KBR disc and scanned between 4000 and 400 cm^{-1}. This test was accomplished for both pure EPR and for the optimum formula [1].

3.1.7. Scanning electron microscopy (SEM)

The scanning electron microscope (SEM) model Inspect 50 FEI, Germany is used to analyze the morphology and surface characteristics of the egg box. It is also capable of detecting drugs that are loaded into the egg boxes [9,10].

3.1.8. Energy dispersive spectroscopy (EDS)

Energy Dispersive Spectroscopy (Axia, Thermoscientic company. Holland) is consider as a main component of scanning together with transmission microscopes that empower a qualitative and semi-quantitative identification of chemical elements in a range of materials due to the X-ray detection of elemental composition of examined sample [11]. During the study two types of the radiations are investigated:continuous radiation which forms the background of the measurement and the characteristic radiation of a specific wavelength and energy amount. SEM-EDS approach enable the determination of the elemental composition and their

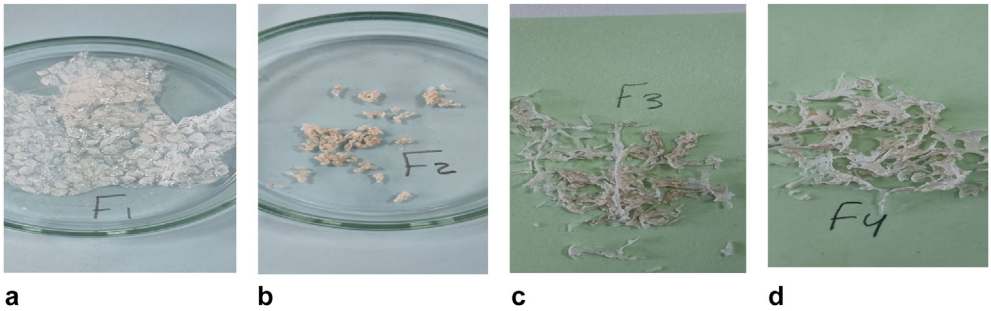

Fig. 5. Pictures photography of physical appearance of F1 (a), F2 (b), F3(c) and F4 (d) respectively.

Table 2. Results of % yield, % drug loading and taste mask test of the prepared formulas.

Formula code	% Yield	% Drug loading	Taste mask test (%drug released in pH 6.8)
Pure EPR 7.5 mg	–	–	57 %
F1	7	Excluded	–
F2	89.5	36	5 %
F3	99	60	3.3 %
F4	95	75	3.2 %

respective percentages in the studied pharmaceutical form. The SEM-EDS approach enables the determination of the elemental composition and their respective percentages in the studied pharmaceutical form. SEM (SEM-EDS) is frequently employed in conjunction with it to discover and identify impurities and degradation products in medicinal compounds. This enables a more comprehensive knowledge of the mechanisms involved in their creation.

It is often employed with SEM (SEM-EDS) which can also locate and identify the impurities and degradation products of the compounds in the drug form, leading to a better understanding of the mechanisms of their formation [12].

4. Result and discussion

4.1. Physical appearance

As depicted in Fig. 5, increasing the concentration of $CaCl_2$ from 0.5 to 1% w/v transforms the shape from a film (flack) structure to irregular spherical particles. This change is attributed to the enhanced crosslinking resulting from the higher concentration of the crosslinker ($CaCl_2$) [8].

4.2. Percentage yield

All formulas exhibited acceptable percentage yields (ranging from 89.5% to 99%), except for F1, which had a significantly low percentage yield of 7%, as shown in Table 2. This poor yield can be attributed to the low concentration of $CaCl_2$,

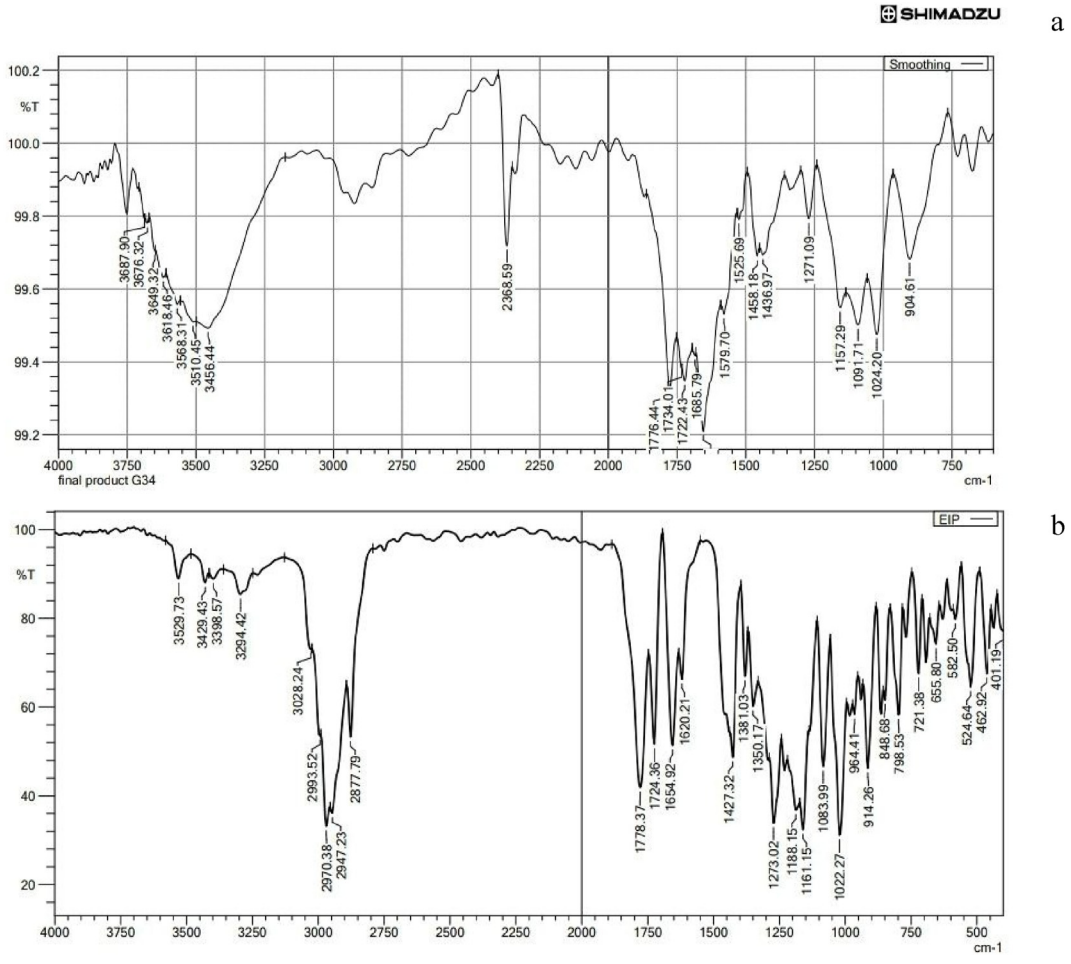

Fig. 6. FTIR for (a) pure EPR. (b) Selected F4.

resulting in a decrease in the crosslinking between Ca^{+2} and Na^{+}-alginate [5,6].

4.3. Drug loading %

During the study, it was observed that the drug loading percentage at the Table 2 ranged from 36% to 75%. This variation may be attributed to the fact that an increase in the drug quantity: polymer ratio increases the likelihood of drug encapsulation through the egg-box mechanism [13].

4.4. In-vitro taste masking test

As shown in Table 2, F2, F3 and F4 successfully masked the bitter taste by significantly reducing EPR release in phosphate buffer saline 6.8 within 1 min (5%, 3.5%, and 3.2% respectively). This indicates that all formulas were successful in masking the bitter taste using 1% Na^{+}-alg and 1% cross linker $CaCl_2$, which formed a hard gel barrier that decreased the release of EPR at the pH of the mouth within 1 min, compared to pure EPR alone [14].

4.5. Selection of the optimum formula

After analyzing the results of all the formulas in Table 2, it was determined that F4 is the optimal formula due to its superior taste masking effect. Additionally, F4 exhibited a greater drug load and an acceptable percentage yield compared to the other formulas.

4.6. FTIR

The functional groups of pure EPR, as shown in Fig. 6a, include an anhydride O-C-O stretching band at 1778.37 cm^{-1}, a C-O ester stretching band at 1724.36 cm^{-1}, and a C-O stretching band at 1654.92 cm^{-1} [15]. In Fig. 4b, these peaks of the functional groups of EPR in the optimum formula (F4) were observed with lower intensity. This can be attributed to the dilution of the drug with polymer, indicating that there was no chemical interaction between the EPR and the Egg box.

4.7. SEM

The irregular morphology of the empty egg box was obtained as demonstrated in Fig. 7a. This morphology is dependent on the concentration of the polymer and the cross linker. As the concentration increases, a more regular and spherical egg box is obtained [16]. Fig. 7 (b, c) shows that the surface of F4 is rough, indicating that the egg box is loaded with the EPR [17].

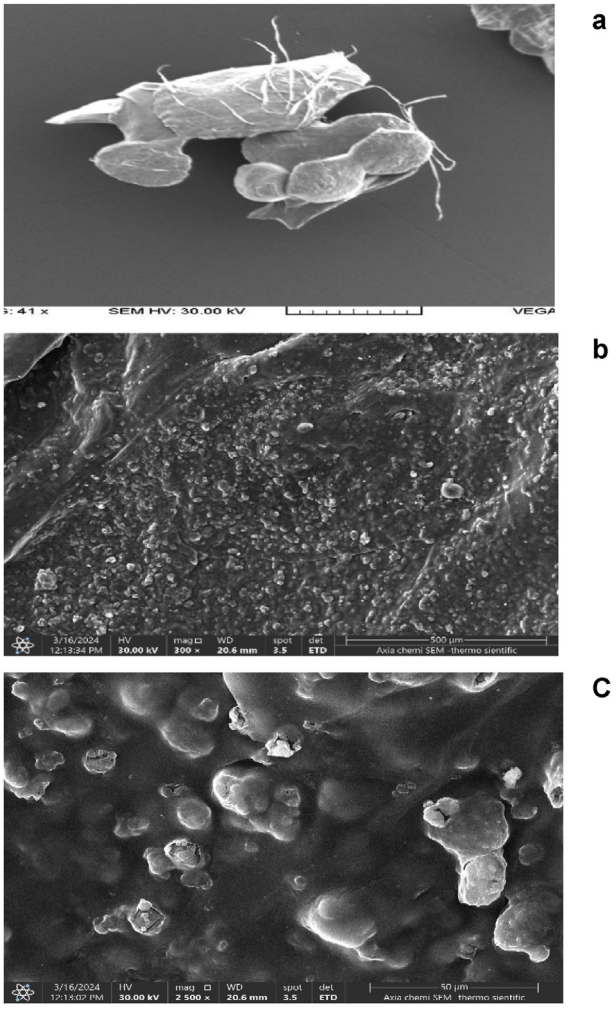

Fig. 7. SEM image of a: empty egg box, b and c: selected F4 using different magnifications.

4.8. EDS

The EDS can be used to study the surface of particles. The EDS scans conducted at various points on the drug form's surface therefore, it

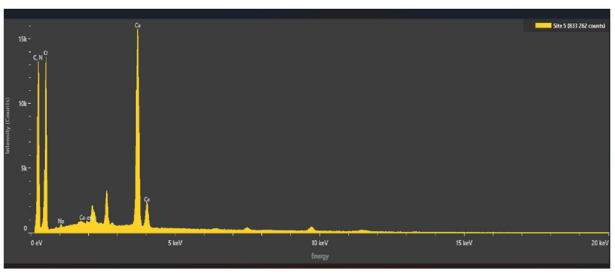

Fig. 8. EDS results of elements of F4.

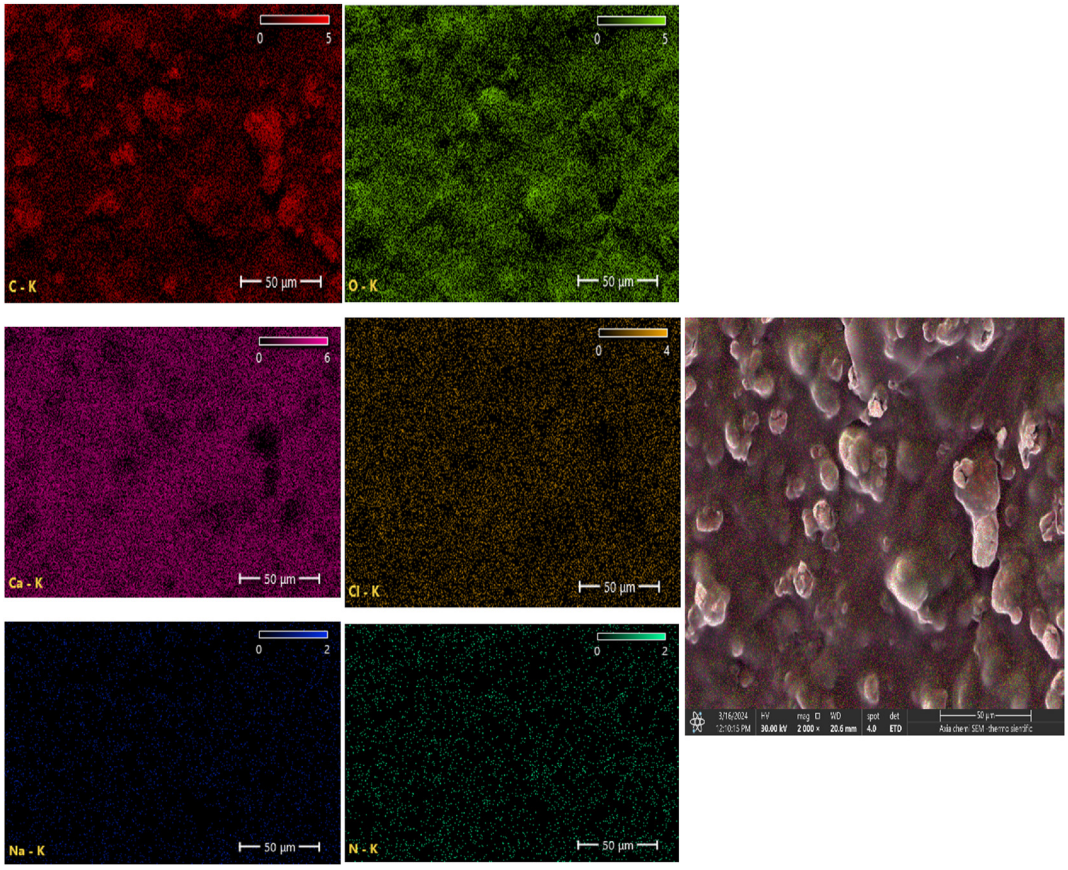

Fig. 9. The results of EDS analysis of F4.

provides more precise and accurate surface imaging and aids in the analysis of contamination brought on by pharmaceutical items that contain particulate debris which result in problems with quality and safety from such an impurity [9]. The current study demonstrates that EDS analysis confirms the existence or absence of contaminants in the analyzed solid dosage form along with the production process, that can provide valuable information in pharmaceutical studies. From EDS results of selected formula (Figs. 8 and 9), it approve the absence of impurities or any drug interaction resulted in sample analyzed since same elements that composed the chemical structure (Table 3) of sample present in the same amount which support the result from FTIR that confirms the absence of drug incompatibility with other constituents such as sodium alginate and calcium chloride [18].

Table 3. Elements of selected formula F4.

Element	Atomic %	Atomic % Error	Weight %	Weight % Error
C	32.0	0.2	24.1	0.2
N	7.4	0.5	6.5	0.5
O	54.6	0.4	54.7	0.4
Na	0.2	0.0	0.3	0.0
Cl	0.7	0.0	1.6	0.0
Ca	5.1	0.0	12.8	0.1

5. Conclusion

According to the findings of this investigation, employing egg box (ionic gelation) method forming calcium alginate beads loaded with eplerenone is an effective approach for masking the very bitter taste of eplerenone through decreasing drug release in the mouth.

Ethics statements

This study was in vitro and does not need an ethical approval from an ethics committee.

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