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Formulation and Evaluation of Prednisolone -Loaded Alginate Beads for Taste Masking

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ABSTRACT

Background: prednisolone (PRD) is a very bitter, corticosteroid drug, acts as immunosuppressant and anti-inflammatory used for treatment of many diseases like asthma and arthritis.

Objective: This study aimed to formulate and evaluate taste masked PRD-alginate beads to increase patient compliance.

Method: PRD taste masked beads were prepared by external ionic gelation technique using sodium alginate (S. Alg) as polymer and 1% calcium chloride as cross linker. The beads were evaluated for their physical properties including general appearance, percentage yield, drug loading, drug content and *in vitro* taste masking. The effect of S. Alg concentration, addition of tween, addition of hydrophilic polymers (Carbopol 940, PEG 4000, HPMC E5 and PVA) on the physical properties of beads was studied

Result: This method was successful in decreasing the release of PRD from beads in phosphate buffer pH 6.8 within 60 seconds. The optimum formula (F6) was obtained by using S. Alg (0.5% W/W) in combination with carbopol 940 in a ratio of 1:1:1 ratio (PRD: S. Alg: Carbopol 940) with percentage yield 88%, drug loading 77%, drug content 98.3 ± 2.1 and 0.77 % ± 0.19 release of PRD in phosphate buffer pH 6.8 within 60 seconds, supposing good taste masking.

Conclusion: It can be concluded that oral preparation of PRD with an acceptable taste is possible by using external ionic gelation technique.

Keywords: Prednisolone, Taste masking, External ionic gelation, Sodium alginate, Calcium chloride and Carbopol 940.

INTRODUCTION

Pediatric, geriatric and other patients who are suffering from difficulty in the swallowing, need a specific oral dosage form like chewable tablets, fast dissolve oral tablet/ film or liquid dosage form. Since some drugs have undesirable taste, taste masking becomes an important way to improve patient compliance. Different techniques are available for taste masking like addition of sweetener and/or flavoring agents, coating with polymer, complexation with resin or cyclodextrin adsorption, chemical reaction like pro-drug and ionic gelation [(1)].

Prednisolone (PRD) is a glucocorticoid acts as immunosuppressant and anti- inflammatory drug which has been widely used for the treatment of allergic reactions like asthma and articria, peritumoral edema [(2, 3)]. It has a bitter taste which decreased the patient's compliance especially children [(4)].

Ionic gelation is a chemical reaction that used to encapsulate the active ingredient by formation of insoluble gel. This method is used for masking of undesirable taste. In this method; alginate salts such as sodium alginate reacts with bivalent metal ion like calcium or barium chloride and form beads (insoluble gel) which contain the bitter active ingredient. Taste masking is obtained by decreasing the drug release in the mouth cavity [(5, 6)] . Thus this study, aimed to mask the bitter taste of PRD by using sodium alginate as polymer cross-linked with 1% $CaCl_2$ to form calcium-alginate beads loaded with PRD by using external ionic gelation method to mask the bitter taste of PRD and improve patient compliance.

MATERIAL AND METHOD

Prednisolone powder (gift from Samarra Drug Industry), sodium alginate (viscosity 5- 40 cps, sigma-Aldrich), un-hydrous calcium chloride (Gainland chemical Co. UK), carbopol 940 (Gainland chemical Co. UK), HPMC E5 (sigma- Aldrich), PEG 4000 (china), PVA (china).

Preparation of PRD- Alginate beads

By using external ionic gelation method; sodium alginate (0.5 or 1 % w/w) and PRD dispersion was prepared in distilled water with different ratios as shown in table (1), with continuous stirring (500 rpm) for about 1 hour at 40 ^{o}C with or without tween 80 or polymers. Later the prepared dispersion was added drop wise to 100 ml of 1% $CaCl_2$ solution using a needle (23-G). The calcium-alginate beads were then separated, rinsed with distilled water, and kept for 24 h in oven for drying at 40 ^{o}C, after that they were stored in a sealed container [(7, 8)] . Physical mixture (PM) for optimum formula was prepared by mixing 1:1:1 (PRD: S. Alg: polymer) ratio by mortar and pestle for 15 minutes for FTIR test.

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Table (1): Taste masking formulation by external ionic gelation method

Formula / Component	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PRD: S. Alg	1:1	1:1	1:2	1:3	1:1	1:1	1:1	1:1	1:1	1:1
S. Alg % (mg)	0.5 (125)	0.5 (125)	0.5 (125)	0.5 (125)	1 (250)	0.5 (125)	0.5 (125)	0.5 (125)	0.5 (125)	0.5 (125)
PRD (mg)	125	125	62.5	41.6	250	125	125	125	125	125
Tween 80 (mg)	-	3.85	1.87	1.24	-	-	-	-	-	-
Carbopol (mg)	-	-	-	-	-	125	-	-	-	125
PEG 4000 (mg)	-	-	-	-	-	-	125	-	-	125
HPMC E 5 (mg)	-	-	-	-	-	-	-	125	-	-
PVA (mg)	-	-	-	-	-	-	-	-	125	-
D.W ml	25	25	25	25	25	25	25	25	25	25
$CaCl_2$ %	1	1	1	1	1	1	1	1	1	1

Evaluation of the prepared beads

General appearance of prepared beads loaded with PRD: Visual appearance of shape and color of prepared beads loaded with PRD.

Percentage yield

The percentage yield for each formula was calculated as the ratio of actual weight of PRD-alginate beads to theoretical weight of mixing materials by following equation [9]:

$$\boldsymbol{yeild}\ \% = \frac{Actual\ weight\ of\ PRD - alginate\ beads}{Theoretical\ weight\ of\ PRD - alginate\ mixture} * 100$$

Drug loading

This test was done by measuring the amount of PRD in the external aqueous solution (1% $CaCl_2$ solution), where the drug concentration was determined by UV – spectroscopy at 242 nm. Percentage drug loading was then calculated by following equation [10]:

$$\boldsymbol{Percentage\ drug\ loading} = \frac{Practical\ drug\ loading}{Theoretical\ drug\ loading} * 100$$

Drug content (drug entrapment)

Drug content was evaluated by adding specific quantity from PRD-alginate beads equivalents to 5 mg of PRD after crushing by mortar and pestle, to 30 ml ethanol and stirred for about 1 hour, then filtered through 0.45 µm membrane filter syringe and after appropriate dilutions the PRD content was measured by using Uv-spectrophotometer at 242 nm. The percentage for drug content was calculated by following equation [11, 12]:

$$\boldsymbol{Drug\ content}\ \% = \frac{Calculated\ drug\ content}{Theoretical\ drug\ content} * 100$$

This test was done in triplicate.

In- vitro taste evaluation

A specific amount of the prepared formulas equivalents to 5 mg of PRD, 5mg drug (as control), was added to 10 ml phosphate buffer pH 6.8 at 37 ^{o}C separately and shaked for 60 seconds. The amount of the drug released was analyzed at 248 nm. This taste was done in triplicate [13].

Selection of the best taste masking formula

The selection of the best taste masking formula depended on the in vitro taste masking test. The formula that gave minimum release of drug in phosphate buffer pH 6.8 within 60 sec. was selected as optimum formula and subjected to further studies [14].

Evaluation of the best taste masking formula

Fourier Transforms Infrared Spectroscopy (FTIR)

The FTIR spectra of pure PRD, taste masking agents, the optimum taste masking formula and its PM were determined to detect if there is any interaction between the drug and the chosen taste masking agents. These spectra were obtained by scanning range 400– 4000 cm^{-1} using infrared spectroscopy (Shimadzu, Japan) [15].

Scanning Electron Microscopy (SEM)

The surface morphology of pure drug, empty beads and loaded beads of the best formula was determined by using SEM (VEGA3Tuscan). The beads were mounted on an appropriate stub and then coated with carbon and gold (100 and 50 Å thickness respectively) sputter module in a vacuum evaporator in an argon atmosphere. The coated samples were then observed under a scanning electron microscope operated at 15 KV [16].

Ethical approval:

The study was approved by the Ethics Board of University of Baghdad.

Statistical Analysis

This study was achieved in triplicate, and to approximation the average of the accurate results was calculated and t-test was used with $p \leq 0.05$ as the minimal significance level was achieved for statistical data analysis.

RESULTS

General appearance of preparation of beads loaded with PRD

In general, all the wet beads were spherical in its shape, but its color was different. It was transparent with formulation containing tween 80 (solubilizing the drug in hydrogel)) as shown in Figure (1), while formulation without tween 80 (the drug was dispersed in hydrogel) was white in its color as shown in Figure (2).

Figure (1): F2 spherical and transparent in color.

Figure (2): F6 spherical and white color

Percentage yield: The percentage yield of calcium-alginate beads loaded with PRD was with a wide variation, as it ranged from 0 % for F1 (failed formula) to 99% as shown in table (2). This wide range was due to different factors as shown later.

Drug loading

Table (2) showed the results of the drug loading in calcium-alginate beads. It ranged from 52% to 98% and this wide range was due to different factors as it will be discussed.

Drug content (drug entrapment)

Drug content of the method the successful formulas (F5- F10) showed acceptable drug content (according to USP) as it ranged from 91.6 to 99% as shown in table (2).

In- vitro taste evaluation

The release of PRD in media with pH 6.8 within 60 sec. was ranged from 0.77 to 3 % (Table 2) with exception of F7 (14.4 %).

Selection of the best taste masking formula

According to the previous results, F6 ((PRD: S. Alg: Carbopol 940 in 1:1:1 ratio)) was selected as the optimum formula, since it showed better taste masking as the lowest drug was released at pH 6.8 within 60 second.

Table (2): Percentage yield, drug content and drug release at pH 6.8 (taste masking) of the prepared beads

Formulas	Yield %	Drug loading %	Drug content* % ± SD (n=3)	Drug release% at pH 6.8 ± SD (n=3)
Pure PRD	-	-	-	55 ±1.2
F1	0	-	-	-
F2	23	94	Excluded	-
F3	29	68	Excluded	-
F4	36	52	Excluded	-
F5	99	70	99.3 ±1.2	1± 0.18
F6	88	77	98.3 ±2.1	0.77 ±0.19
F7	72	77	91.6 ±1.6	14.4 ±1.1
F8	95	98	97.3 ±1.6	3 ±0.73
F9	72	83	96.5 ±1.8	1.6 ±0.18
F10	73	84	96 ±1.6	2.7 ±0.14

* The results of drug content were based on drug loading.

Evaluation of the best taste masking products

FTIR

The FTIR spectrum of pure PRD, S. Alg, carbopol 940, its PM and the optimum formula (F6) were showed in Figures (3, 4, 5, 6 and 7) respectively.

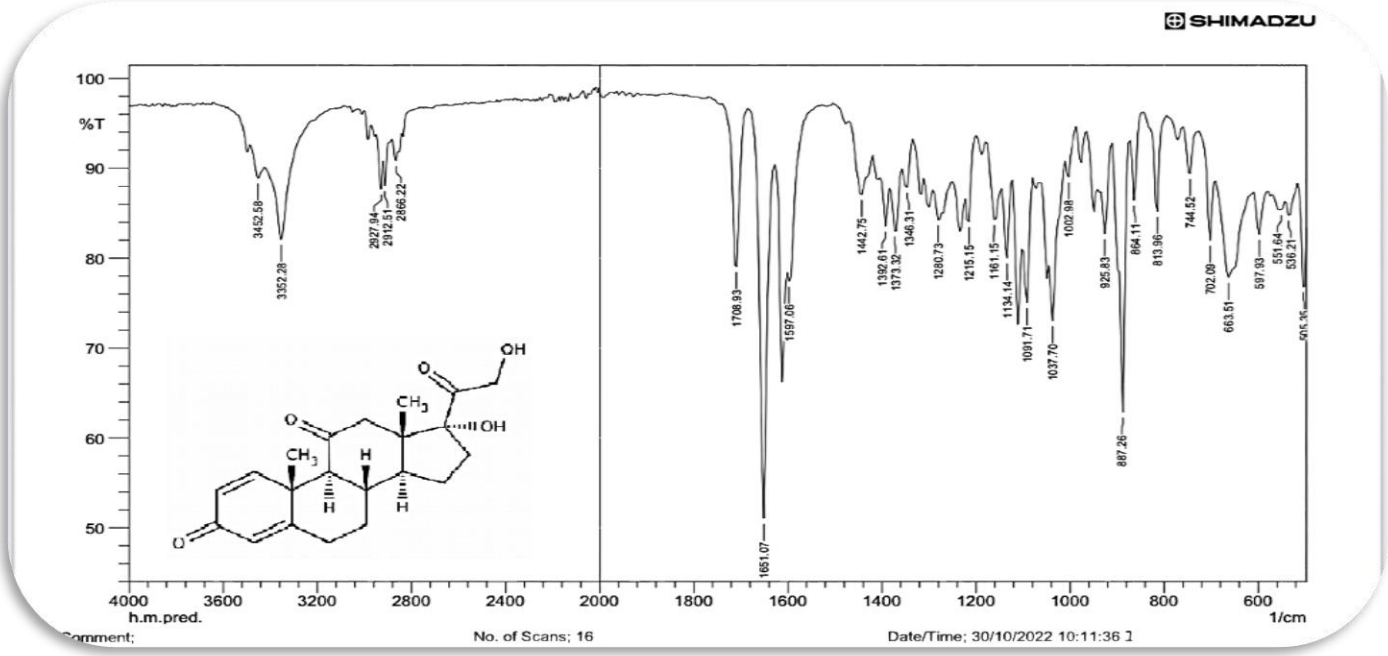


Figure (3): FTIR spectrum for pure PRD powder

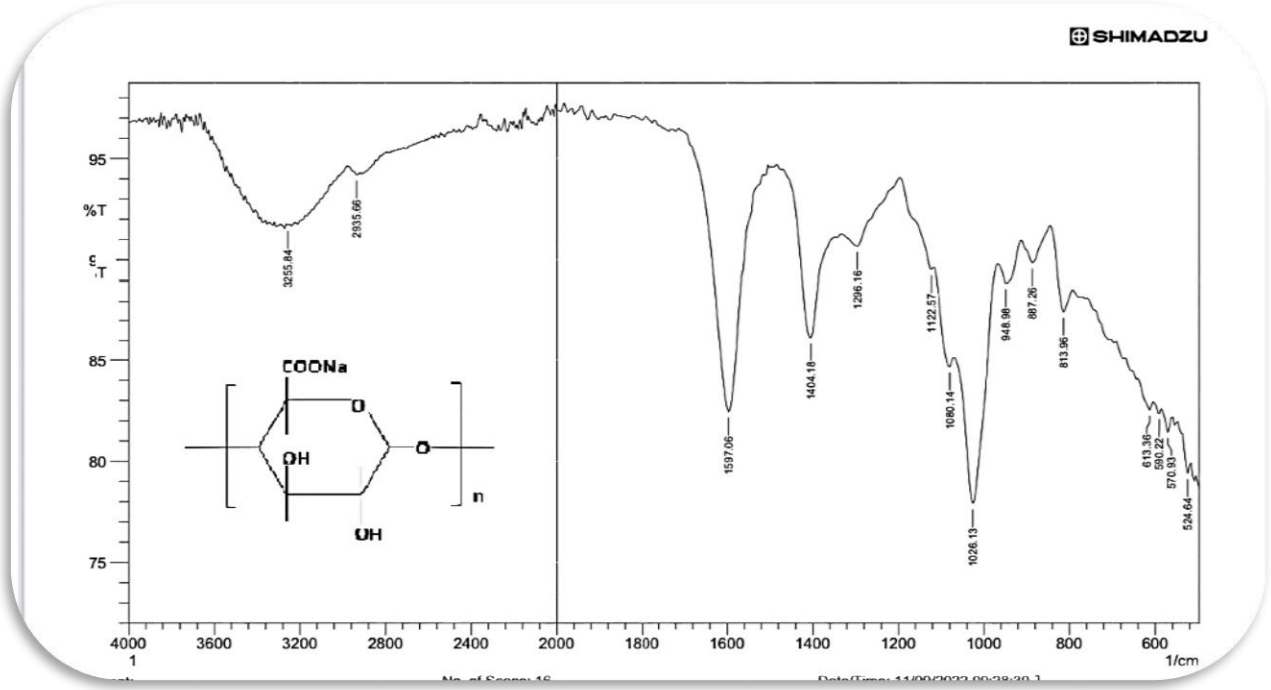


Figure (4): FTIR spectrum for pure S. Alg powder.

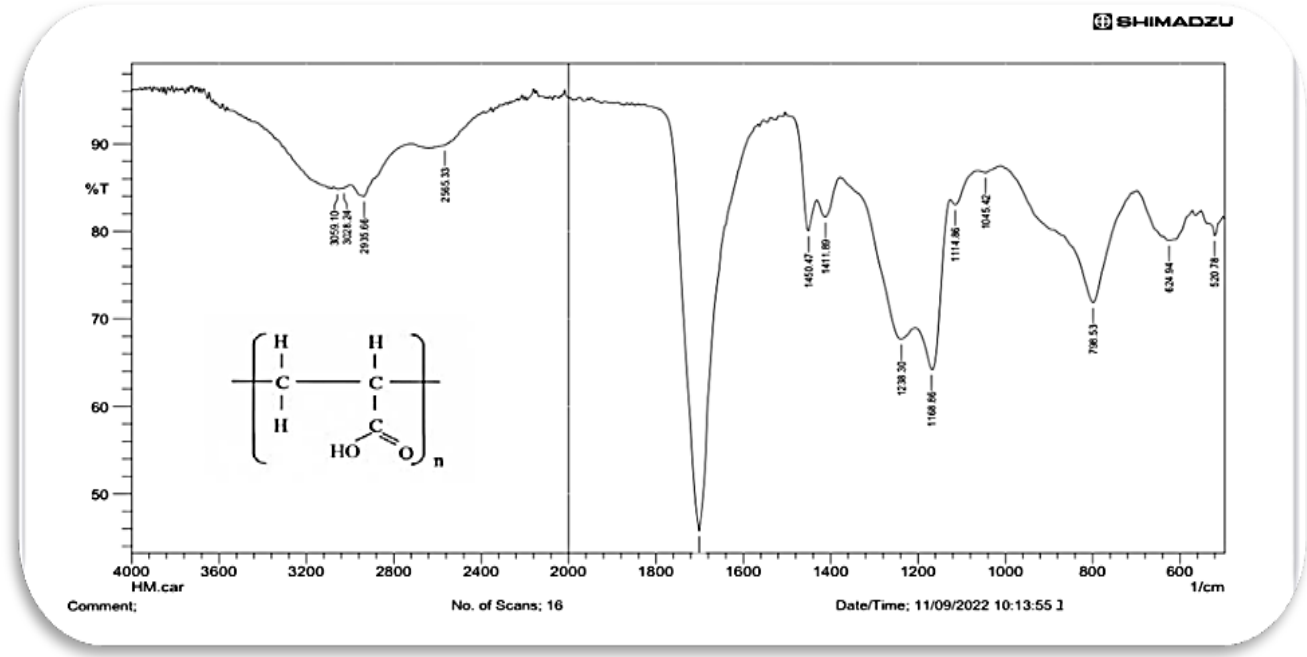


Figure (5) FTIR spectrum for pure carbopol 940 powder

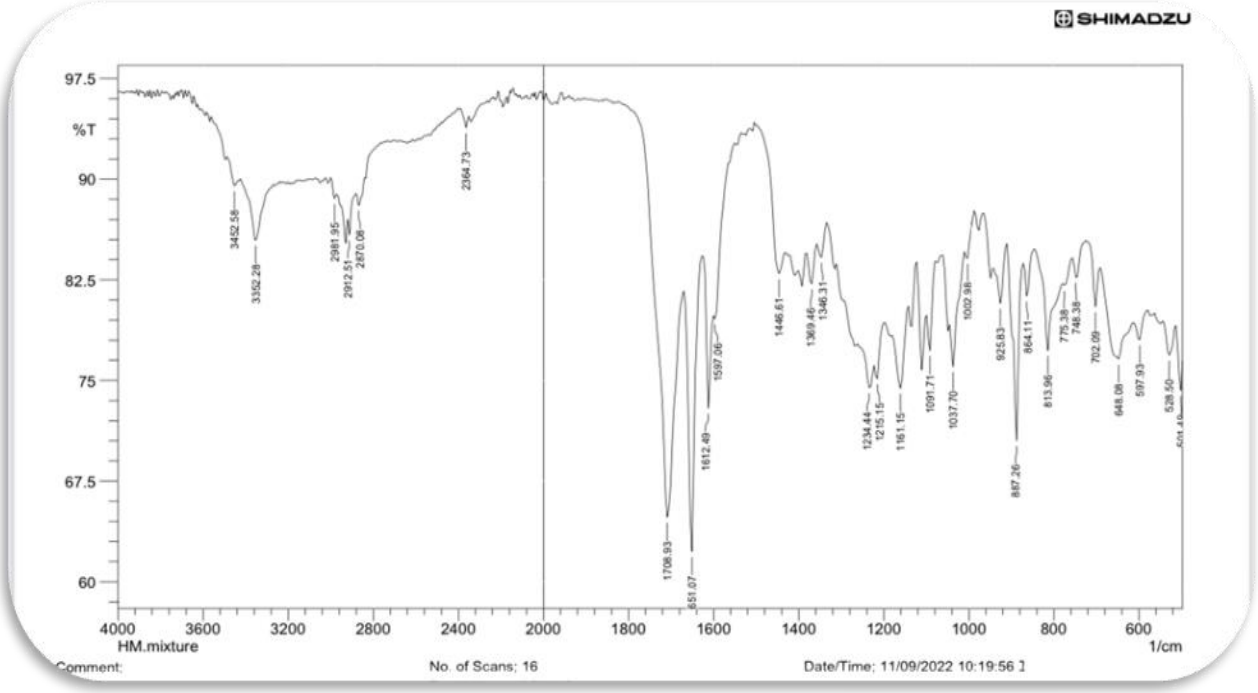


Figure (6): FTIR spectrum for PM

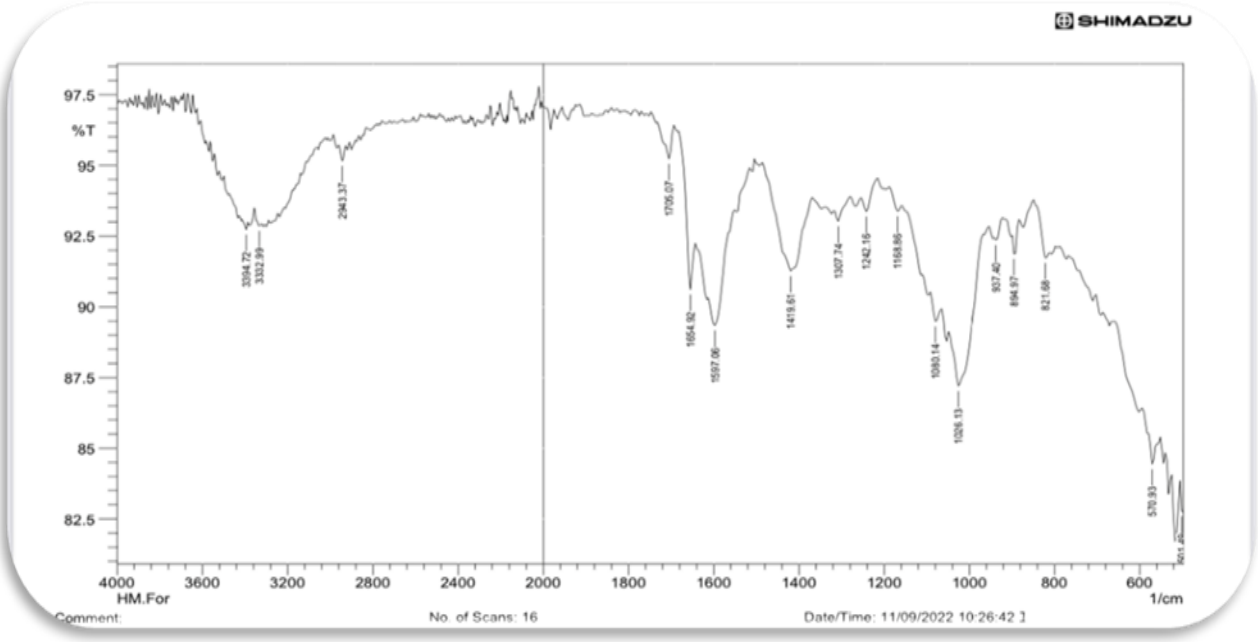


Figure (7): FTIR for optimum formula (F6)

SEM

SEM of the f6 appeared irregular spherical in shape after drying, as shown in figure (8). In addition SEM detect the surface of empty beads, which showed rough surface as shown in figure (9 a), while loaded beads showed smooth surface (Figure 9 b) and by this difference, it could be compared between empty and loaded beads by using SEM.

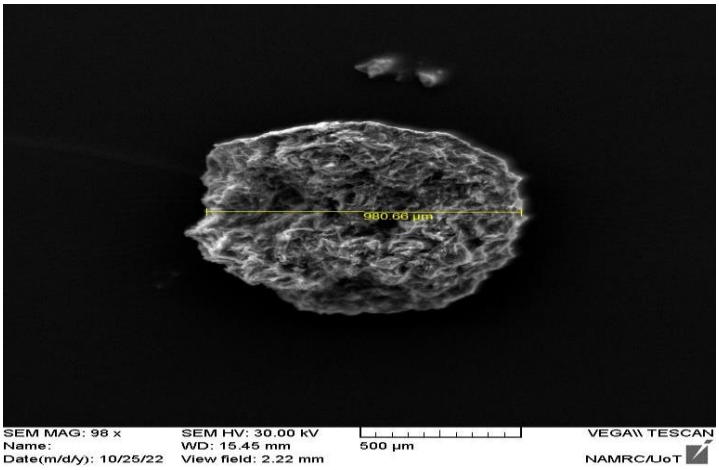
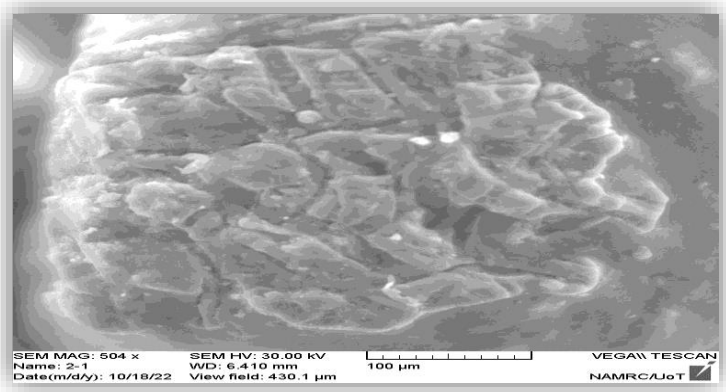
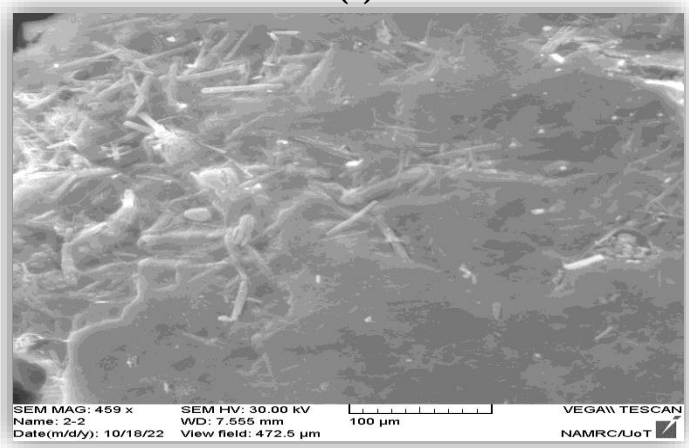


Figure (8): SEM of PRD- alginate beads (F6).



(a)



(b)

Figure (9): (a); surface of empty bead. (b); surface of loaded bead

DISCUSSION

Factors affecting percentage yield, drug content and taste masking of PRD

Effect of tween 80 addition

Tween 80 act as surfactant (solubilizing agent) used to solubilize PRD in sodium alginate 0.5% (w/w) hydrogel to prevent the precipitation of the drug in the hydrogel. This trial was successful in the preparation of transparent beads of, F2, F3 and F4 (all had the same PRD: Tween 80 ratio of 1:0.03 (w/w)) compared to F1 as shown in Figure (1), but their percentage of yield was still practically insufficient as shown in Table (2).

Effect of drug: polymer ratio

In the external ionic gelation method (F2- F4); it was found that decreasing the amount of drug: polymer ratio; resulted in decreased drug loading as shown in Table (2). This result, can be attributed to less amount of drug available for encapsulation [9]. These formulas were excluded from further study as their yield was also low.

Effect of sodium alginate concentration in hydrogel

As shown in Table (2), there was no yield obtained from F1 (0.5 % S. Alg) as its low viscosity resulted in precipitation of PRD. A homogenous dispersion of PRD was obtained by increasing the concentration of S. Alg to 1% (F 5) that can be dropped into $CaCl_2$ solution, which resulted in high production yield of beads (99%) due to increase in the cross linking of S. Alg with calcium ion [17]. Good taste masking of PRD was obtained due to this cross-linking as more drug remained entrapped within the beads that resulted in decreased drug release at pH 6.8 [18].

Effect of addition of hydrophilic polymers to sodium alginate hydrogel

Table (2) showed that addition of hydrophilic polymer (F6- F9) increased the percentage yield and drug loading compared to F1. This may be due to presence of the polymer that caused higher viscosity of S. Alg hydrogel, preventing loss of the drug and generated a dense internal structure with white and uniform shape of beads as shown in figure (2) [19, 20].

The bitter taste of PRD was masked at acceptable degree as there was significant decrease in the release ($P<0.05$) of PRD at salivary pH of 6.8 within 60 second compared to the drug (control). Since S. Alg in presence of Ca^{+2} and polymers formed physical barrier (bead) that decreased its release [21].

Less efficient taste masking was obtained by F7 since significantly ($P<0.05$) higher release of PRD was obtained by using PEG compared to other polymers. This result can be explained to be due to the presence of the freely soluble PEG 4000 that may form a porous beads with crevices which allowed the release of drug [22].

FTIR

The FTIR spectrum of pure PRD was shown in the figure (3) that presented characteristic bands at 3452 and 3352 cm^{-1} for (OH involved in intermolecular association), 1651 and 1708 cm^{-1} for two (C=O) stretching. These results are in agreement with previous studies [14, 23].

FTIR spectrum for S. Alg (Figure (4) showed a large absorption band in range 3600- 3000 cm^{-1} that was due to stretching OH groups, -CH broad band at 2935 cm^{-1}, two main peaks for symmetric and asymmetric stretching of (COO^{-}) at 1597 and 1404 cm^{-1} respectively, which are specific for ionic binding. 1080 and 1026 cm^{-1} for stretching of C-C and C-O with high intensity and three vibration bands at 984, 887 and 813 cm^{-1}, which are specific for guluronic and mannuronic acid groups that constitute the S. Alg [24, 25].

the FTIR spectrum of carbopol (Figure (5) showed main bands at 3059-2935 representing O-H stretching vibration intra-molecular H-bonded and 1714 cm^{-1} for carbonyl stretching [26, 27].

The FTIR for PM was shown in figure (6), no change in the major peaks of the constituents indicating no interaction between them in dry condition [28, 29].

The last analysis for optimum formula F6 (Figure (7) showed a broad band at 3600- 3000 indicating the presence of hydrogen bonds between its constituents. Also the main peaks of PRD (1708 and 1651 cm^{-1}) were shifted to 1705 and 1654 cm^{-1} respectively with decreased intensity that may indicate an interaction of PRD with the constituents of the formula [14, 26].

Furthermore, the small shifts of carboxyl groups (S. Alg) and those specific for guluronic and mannuronic acid groups with decreased intensity may indicate replacement of Na^{+1} in S. Alg with Ca^{+2} of the calcium chloride (cross linker), which confirm the crosslinking reaction [30, 31].

SEM

In general the formation of beads occurred by reaction of Ca^{+2} ion with alginate so, the concentration of alginate affects the morphology of beads. As concentration of alginate less than 5%; the morphology showed irregular shape as shown in Figure (8), and that's because insufficient carboxyl group (in S. Alg) for crosslinking with Ca^{+2} ($CaCl_2$). Thus, the shrinkage of beads' surfaces was developed after drying. Therefore, the shape of calcium alginate gels depended on the viscosity of the sodium alginate solution [32].

Also the SEM approved drug loading as the empty beads (Figure 9-a) showed rough surface, while the loaded beads (Figure 9-b) showed smooth surface with crystalline fibers, which may be resulted from interaction of PRD with alginate and this result confirmed the FTIR results [19, 31, 33].

CONCLUSION

Taste masked PRD beads can be successfully prepared by external ionic gelation method using low concentrations of S. Alg 0.5% (w/w) and 1% (w/w) $CaCl_2$ as cross-linked in combination with 0.5 % (w/w) hydrophilic polymers.

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