Optimization Of Swelling, Drug Loading And Release From Natural Polymer Hydrogels

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Abstract. The current work deals with synthesis of natural polymer hydrogels (Sodium alginate-Chitosan- Arabic Gum) as beads. The beads are formulated with different polymer proportions depending on the experimental central composite (design) Response Surface Methodology (RSM) has been used. The degree of swelling in acidic and neutral mediums was investigated, analyzed, modeled and optimized statistically. A typical drug (Allopurinol) was loaded by using optimized polymer formulations. The loading capacity and the in vitro release profiles were estimated. The shape and morphological analysis for the beads before and after drug releasing have been investigated also by using Scanning Electron Microscope. The results obtained confirmed that Arabic Gum content was a significant parameter in the swelling processes regardless the pH of the swelling media. Thus, swelling indices of the beads were higher in acidic medium (pH 3.9) compared to that once in (pH 7.1), to indicate a pH-sensitive swelling behavior. An optimum RSM results for swelling indices of 504.98 % and 207.97 % were obtained in acidic and neutral medium respectively. The in vitro drug release showed equilibrium after 12 hours where as (66.1 - 85.7 %) and (44 - 54 %) was released at pH 3.9 and 7.1 respectively. The SEM analysis of the polymer beads confirmed that the beads had lost their shape due to erosion and swelling activities after releasing of the drug.

Keywords: Polymer gels, Drug Release, Morphology, Response Surface Methodology, Swelling Index

1. Introduction

Natural polymers have demonstrated significant utility in the medical and pharmaceutical areas in the field of drug formulations and drug delivery devices for a long time [1,2]. Polymers are commonly used as carriers of bioactive agents, including drugs, to improve the release kinetics, to modify transport or circulation half-life characteristics of the pharmaceutical agents as well as to allow for passive and active targeting. They are also used as a bioactive drug that can provide its own therapeutic benefit [3,4,5].

Polymer devices can be categorized as diffusion-controlled, solvent-activated, chemically controlled (biodegradable), or externally-triggered systems [6]. In diffusion-controlled systems, a drug is dissolved or dispersed in a non swellable or fully swollen matrix that does not degrade during its therapeutic life. In solvent-activated systems, drugs are loaded into dehydrated hydrophilic polymers or hydrogels in presence of a plasticizing aqueous solvent. Chemically controlled biodegradable and bio erodible polymers are used as carriers in biodegradable systems, while targeted drug delivery tends to deliver drugs to a particular location, one way of this technology is coating the drug with magnetic nanoparticles that are able to trigger drug release when they are exposed to an external oscillating magnetic field [7]. Polymers serving as drug carrier should possess have certain. They have to be water soluble, nontoxic and they don’t have to produce any immune response [8]. Drug carriers include...
hydrogel polymers which are cross-linked networks containing hydrophilic groups but they are not water soluble [9]. Hydrogels have a collection of significant properties that are desirable for diverse application. The properties include flexibility, versatility (fabrication), variety (in composition), high-tuneable in physical, chemical, and biological properties, absorption capacity, swelling behavior, stability and degradation, bio-adhesion and bioactivity [10] permeability [11]. On the other hand, improving controlled and extended release of drugs, comparing to that once obtained by using one polymer system, could be achieved by using polymer composite systems [12, 13]. Polymer are composites comprised of various chemical composition. Functionality and degradation behavior could be carefully designed to attain the optimum performance for drug delivery [14]. Allopurinol (1H-pyrazolo [3, 4-d] pyrimidin-4(2H)-one), with the trade names: aloprim, lopurin, zyloprim is used in the treatment of gout disease and high levels of uric acid by inhibiting the action of xanthine oxidase enzyme that catalyze the production of uric acid in blood. The drug half-life is 1-2 hours, and the usual oral dose 100, 200, 300 mg to be taken once a day, as it has a short half-life it is suitable for sustained release drug delivery [15, 16]. Fig. 1 shows schemes of polymer components and drug.

In the present work, a multi-component polymer system (Chitosan- Sodium Alginate- Arabic Gum) hydrogel composite was designed, formulated and manufactured as beads for drug carrier. The first polymer is Chitosan, it is a cellulose-like biopolymer. It is the deacylated form of chitin. It consists predominantly of unbranched chains of β-(1→4)-2-amino-2-deoxy-D-glucose. The second is Sodium Alginate. It is the sodium salt of alginic acid. Alginate is a gelling polysaccharide or the sodium salt of a linear polymer of β-(1→4)-D-mannosyluronic acid and α-(1→4)-D-gulosyluronic acid residues, with proportions vary with the source and state of maturation of the plant. The third polymer is Arabic Gum, which is a complex and variable mixture of arabinogalactan oligosaccharides, polysaccharides and glycoproteins. They are mainly formed by chains of 3, 6-linked β-D-Galactopyranose substituted in position 6 by side chains of 3-linked α-L-arabinofuranose.

Polymer composite formulations were synthesized according to an experimental central composite design via RSM software. The swelling behavior of the polymer composite beads was investigated and analyzed statistically. The stability and degree of swelling in acidic and neutral mediums was modeled and optimized. The typical drug was loaded in the polymer composites formulations. The loading capacity and in vitro release profiles were estimated. The shape and morphological analysis for the beads before and after drug releasing have been investigated by using a Scanning Electron Microscope (SEM).

![Figure 1. Schemes of Polymer Components and drug](image_url)
2. Experimental

2.1. Materials
Chitosan, Sodium alginate, Arabic Gum and all other chemicals were purchased from Sigma aldrich. Glutaraldehyde was obtained from India institute of Technology, ROORKE, India. Allopuurinol was obtained from Nineveh Drug Factory (NDF).

2.2. Preparation of (Sodium alginate-Chitosan- Arabic Gum) beads
Sodium alginate-Chitosan- Arabic Gum beads were formulated according to the experimental design shown in Table 1. The ratio of Chitosan/ Alginate was kept constant 1:1, while the concentration of Arabic Gum was different in each experiment. For example: 1g composite beads of 40 % Arabic Gum is composed of (30% Chitosan, 30% Alginate, and 40% Arabic Gum).

The preparation of beads was performed according to a general procedure with some modifications [17, 19, 20]. Sodium Alginate and Arabic Gum solutions were prepared separately by dissolving predetermined amount of the materials in (10 ml) distilled water at 30°C with stirring (150 rpm) until homogenous solutions were obtained. Chitosan solutions were prepared by dissolving a predetermined amount of Chitosan powder in 10 ml 2% acetic acid at room temperature with stirring (150 rpm) until a homogenous solution was obtained. The solutions of Sodium Alginate and Arabic Gum were carefully mixed, then Chitosan solutions were added with consistent stirring. A combined solution of (200 µml) Glutaraldehyde and (100 µml) Concentrated HCl was added to the solutions of polymers with stirring (150 rpm) until the composite beads were obtained. The aim of the continuous stirring is to improve the mechanical strength of the beads and to prevent their aggregation. The beads were filtered, washed with hot and cold water and vacuum dried at (35 °C). The dried beads were doubly wrapped in an aluminum foil and kept in a desiccator till further use.

2.3. Infrared study
In order to confirm the interactions between the polymeric complex and the drug, infrared spectra (IR) of chitosan, alginate, Arabic gum and the drug were recorded by Fourier Transform-Infrared (FTIR) spectrophotometer supported by (Thermo Scientific) NICOLET iS10 by using the attenuated total reflection (ATR) method. Samples were scanned from 600 to 4000 cm\(^{-1}\) at a resolution of 4 cm\(^{-1}\).

2.4. Swelling study
Response Surface Methodology (RSM) was used for optimizing and modeling the impact of incubation time and temperature on swelling index of the adopted hydrogels. The statistical analysis procedure of Statgraphics plus for Windows software (5.1 version) for experimental design and data treatment was used. The RSM normally allow identifying the effects of operating parameters (independent variables Xi) on different responses Yj (dependent variables). A central composite design consisting of 16 experiments runs with three replicates at the center point was established. The mathematical empirical model applied is:

\[
Y = \beta_0 + \sum_{i=1}^{n} \beta_i X_i + \sum_{i=1}^{n} \beta_{ii} X_i^2 + \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \beta_{ij} X_i X_j + \varepsilon \quad \text{Equation (1)}
\]

Where: \( Y \): is the response or dependent variable; \( X_i \) and \( X_j \) are the independent variables; \( i \) and \( j \) are the indices; \( \beta_0, \beta_i, \beta_{ii}, \beta_{ij} \) are the regression coefficients; and \( \varepsilon \) is the random error of the factor

The analyses of variance (ANOVA) were used to determine significant differences between the independent variables (p<0.05). The two-dimensional (2D) contour plot provides a distinctive illustration of values of the response; whereas, the 3D response surface plot is very helpful in understanding the main interaction effects of the independent variables.
The identification of the impact of variables on various responses is illustrated in Pareto chart. The vertical line in the Pareto chart determines the effects that are statistically significant at 95% as confidence level. Surface methodology plots are used to optimize various responses. The coded and actual levels of independent variables are used in experimental design. The values of swelling indices at different time for the hydrogels at pH 3.9 and 7.1 are listed in Table 1 and Table 2 respectively.

**Table 1.** The independent variables, coded and actual levels, and values of the responses at pH=3.9

| Coded level | -α | -1 | 0  | +1 | +α |
|-------------|----|----|----|----|----|
| Arabic Gum content (wt. %) | 6.4 | 20 | 40 | 60 | 74 |
| Temperature (°C) | 25 | 30 | 37.5 | 45 | 50 |
| Time (min.) | 29.3 | 60 | 105 | 150 | 181 |

Table 1. The independent variables, coded and actual levels, and values of the responses at pH=3.9

| Exp. No. | Independent Variables | Response Swelling % |
|----------|-----------------------|---------------------|
|          | Arabian Gum (% wt.)   | Temp. (°C) | Time (min.) | Swelling | Time |
|          |                       | 30 min. | 1h | 2h | 4h | 8h | 24h |
| 1        | 40                    | 37.5 | 105 | 90.78 | 126.95 | 132.62 | 134.75 | 136.17 | 179.43 |
| 2        | 40                    | 25   | 105 | 69.40 | 105.97 | 113.43 | 118.66 | 118.66 | 123.13 |
| 3        | 40                    | 37.5 | 105 | 88.95 | 127.65 | 131.92 | 135.10 | 138.01 | 179.10 |
| 4        | 40                    | 50   | 105 | 138.96 | 179.22 | 184.42 | 188.31 | 197.40 | 207.79 |
| 5        | 60                    | 30   | 60  | 13.80 | 18.61  | 23.15  | 27.43  | 28.92  | 30.00  |
| 6        | 60                    | 45   | 150 | 12.90 | 15.8   | 19.70  | 20.3   | 24.10  | 25.00  |
| 7        | 40                    | 37.5 | 29.3 | 158.14 | 169.77 | 172.09 | 176.74 | 179.07 | 186.05 |
| 8        | 74                    | 37.5 | 105 | 2.51  | 2.93   | 3.74   | 5.11   | 6.32   | 6.50   |
| 9        | 20                    | 45   | 60  | 124.71 | 131.76 | 134.12 | 135.29 | 145.88 | 152.94 |
| 10       | 20                   | 30   | 150 | 132.56 | 141.86 | 153.49 | 165.12 | 179.07 | 227.91 |
| 11       | 40                    | 37.5 | 181 | 71.88  | 76.56  | 76.56  | 79.69  | 82.81  | 87.50  |
| 12       | 20                    | 30   | 60  | 155.32 | 174.47 | 176.60 | 195.74 | 325.53 | 385.11 |
| 13       | 60                    | 45   | 60  | 16.84  | 20.91  | 25.13  | 29.60  | 30.52  | 33.00  |
| 14       | 60                    | 30   | 150 | 9.62   | 10.93  | 15.11  | 18.54  | 19.62  | 20.00  |
| 15       | 6.4                   | 37.5 | 105 | 152.44 | 185.37 | 186.59 | 191.46 | 267.07 | 332.93 |
| 16       | 20                    | 45   | 150 | 115.63 | 138.28 | 147.66 | 153.91 | 150.00 | 153.91 |

α is the (axial distance)=$\sqrt{2^k}$, k is the number of orthogonal design variables (in this case, k=3).

**Table 2.** The independent variables, coded and actual levels, and values of the responses at pH=7.1

| Exp. No. | Independent Variables | Response Swelling % |
|----------|-----------------------|---------------------|
|          | Arabian Gum (% wt.)   | Temp. (°C) | Time (min.) | Swelling | Time |
|          |                       | 30 min. | 1h | 2h | 4h | 8h | 24h |
| 1        | 40                    | 37.5 | 105 | 53.06 | 106.12 | 107.14 | 113.27 | 114.29 | 116.33 |
| 2        | 40                    | 25   | 105 | 59.00 | 97.00  | 99.00  | 105.00 | 123.00 | 185.00 |
| 3        | 40                    | 37.5 | 105 | 55.22 | 105.76 | 107.98 | 113.67 | 115.11 | 116.45 |
| 4        | 40                    | 50   | 105 | 77.33 | 130.67 | 133.33 | 138.67 | 140.00 | 146.67 |
| 5        | 60                    | 30   | 60  | 7.21  | 9.45   | 12.52  | 16.78  | 19.23  | 20.00  |
The dynamic swelling study of the prepared beads was carried out by mass measurement as a function of pH using 50 ml phosphate buffer solutions (pH 7.1 and 3.9). The degree of swelling was measured gravimetrically by weighing the particles prior and after swelling. The polymer beads were removed from the buffer solution, carefully blotted with tissue paper and weighed. The degree of swelling (swelling index) was calculated by the formula:

\[ \% S_w = \left( \frac{W_t - W_0}{W_0} \right) \times 100 \]  

Equation (2)

Where \( S_w \) is the swelling index, \( W_t \) and \( W_0 \) are the weights of the swollen polymer beads at time t and the weight of the dry polymer beads respectively.

2.5. Drug Loading

A typical drug “Allopurinol” was used in this study. Allopurinol is an oral drug used to treat gout or kidney stones, and to decrease levels of uric acid and its complications. The drug was loaded in the polymer beads by solvent – evaporation method. Different amounts of Allopurinol (50, 100, 150, 200, 250, 300 mg) were dissolved separately in (10 ml) methylene chloride. The drug solutions were added to the solution of the optimum polymer beads (20% gum) with the required amount of gluteraldehyd (200 µml) as a crosslinking agent and (100 µml) conc. HCl with stirring (150 rpm) to form a stable oil/water emulsion system at 30±1\(^\circ\)C. Stirring was continued until the hydrogel formed. The solvent was evaporated; the hydrogels were filtered, washed with hot and cold water and vacuum dried at 35°C.

2.6. Vitro Releasing Study

The release studies were conducted by keeping different weights (25-50-75-100-125-150 mg) of Allopurinol loaded polymer hydrogels in 50 ml of phosphate buffer solution (pH 3.9 and 7.1) for different time intervals at 37\(^\circ\)C ±2 in constant temperature water bath (Lab Tech LSB-015S). The amount of drug released was analyzed by using UV-VIS spectrophotometer (Perkin Elmer Lambda) at 250nm. Each release experiment was carried out in three times and their averages were calculated. The calibration curve of allopurinol was estimated by analyzing standard solutions of the drug with different concentrations (2-10 mg/ml) in phosphate buffer solution (pH 3.9 and 7.1) by using UV-VIS spectrophotometer (Perkin Elmer Lambda) at 250 nm.

3. Results and Discussion

The chemical interactions between chitosan, alginate, arabic gum, allopurinol and crosslinking agent GA (glutaraldehyd) were investigated by using FTIR spectrum as shown in Fig. 2. Alginate spectrum shows strong peak at 1595 cm\(^{-1}\), which belonged to the carboxylate group (C=O). In addition, a broad peak was observed at 3242 cm\(^{-1}\), corresponding to the -OH group. The asymmetric stretching peaks at 1082–1023 cm\(^{-1}\) belonged to (C-O-C) whereas the symmetric stretching frequency of the carboxyl
group was observed at 1407 cm$^{-1}$. Chitosan showed two peaks at 3350 cm$^{-1}$, 3286 cm$^{-1}$ (O-H and N-H stretching vibrations), 2872 cm$^{-1}$ (C-H stretch), 1651 cm$^{-1}$ (amide I), 1587 cm$^{-1}$ (N-H bending of amine) and 1026 cm$^{-1}$ (skeletal vibration of C-O-C stretching frequency). Arabic gum showed tremendous peaks at 3279 cm$^{-1}$ (O-H), 2904 cm$^{-1}$ (C-H stretch), 1600 cm$^{-1}$ (O-H bending), 1019 cm$^{-1}$ (skeletal vibration of C-O-C) respectively. Allopurinol showed distinctive bands at 3170-3098 cm$^{-1}$ at high frequency belonged to (N-H) stretching band of secondary amine, at 3040 cm$^{-1}$ (C-H) stretching vibration of pyrimidine ring. Very strong band at 1694 cm$^{-1}$ indicating C=O stretching vibration of the keto form of 4-hydroxy tautomer. Also the strong bands at 1583-1477 cm$^{-1}$ are attributed to (N-H pyrazole and pyrazole stretching ring). Bands at 1388-1366 cm$^{-1}$ denote $\nu$(C-C) + $\nu$(C-N) + $\nu$(C-O) $\nu$(pyrimidine ring) respectively \[21\].

The complex spectrum of (chitosan-alginate-gum-allopurinol) showed peaks at 1594 cm$^{-1}$ and at 1077 cm$^{-1}$ because of imine (C=N) formation (crosslinking of chitosan with GA) and acetyl formation (crosslinking of sodium alginate with GA) respectively, while the characteristic peaks of allopurinol did not show any shift and this proves that the drug was intact in the formulation and did not react either with polymer or the crosslinking agent \[20\].

![Figure 2. FTIR spectra of (a) Chitosan, (b) Sodium alginate, (c) Arabic gum, (d) allopurinol, (e) chitosan-alginate-gum (chi-alg-gum) physical complex, (f) chi-alg-gum-allopurinol complex](image)

The experimental results concerning the impact of swelling time and temperature at different time intervals on degree of swelling for the prepared hydrogels at acidic and neutral medium (pH 3.9 and 7.1) are shown in table 1, table 2, Fig. 3 and Fig. 5 respectively. The swelling indices obtained after 24 hours from the swelling process were analyzed using Response Surface Methodology (RSM). The RSM analysis results are shown in Fig. 4 and Fig. 6 respectively.
Figure 3. Swelling index versus swelling time for the polymer beads in phosphate buffer solution pH

(A). Pareto chart for swelling index  
(B). General trends

(C). Response surface  
(D). Contour plots

Figure 4. Pareto chart (A), general trends (B), response surface (C), Contour plots (D) for degree of swelling of the prepared hydrogels at pH 3.9
Figure 5. Swelling index versus swelling time for the polymer beads in phosphate buffer solution pH (7.1)

(A). Pareto chart  
(B). General trends

(C). Response surface  
(D). Contour plots

Figure 6. Pareto chart (A), general trends (B), response surface (C), Contour plots (D) for degree of swelling of the prepared hydrogels at pH 7.1

The swelling behavior of the polymer beads of different formulations in acidic and neutral medium showed in Fig. 3 and Fig. 5 respectively. The swelling profile in acidic medium (Fig. 3) illustrated
four zones. The swelling degree and rate of swelling increases sharply within the first two hours followed by stagnant step up to the fourth hour from starting the swelling process, then it starts to augment steeply up to the eighth hour from starting the swelling, then taking a semi flat shape to equilibrium. The values of the swelling indices and the swelling rates for the polymer beads seemed to depend on the beads formulation as well as the temperature and time of swelling. However, swelling capacity is inversely proportional to the beads crosslinking density [21-23].

The swelling profiles for the polymer beads in neutral medium (Fig. 5) showed different trends. It illustrated three zones. Within the first two hours the swelling degree and rate increases sharply to be followed by less remarkable stagnant behaviour for the next hour. Then, it resumed increase reaching to approximate equilibrium after four hours from the start of swelling process. The values of the swelling indices and the swelling rates for the polymer beads depended also on the beads formulation as well as the temperature and time of swelling.

The RSM analysis of the swelling process gave detailed information on the significance of the swelling conditions as well as the optimum conditions at which maximum swelling capacity could be obtained. The significance of the operating variables is identified by Pareto charts in the first plots illustrated in Fig. 4 and Fig. 6.

Pareto charts showed that the Arabic Gum content is the only significant parameter in the swelling process. The swelling time and temperature showed no significance effects regardless the pH of the swelling medium. The standardized effect plots (general trends) showed that the swelling indices for the hydrogels in both acidic and neutral media was decreasing with the increasing of Arabic Gum content, temperature and swelling time. In spite of that the plots showed similar trend, more sharp and remarkable decrease in swelling index was observed in acidic medium compared to the neutral.

The swelling indices of the beads were higher in acidic (pH 3.9) medium compared to that one in phosphate buffer (pH 7.1), showing a pH-sensitive swelling behavior. The swelling behavior of the beads in acidic medium could be attributed to the high hydrophilic properties of the hydrogels polymers chains due to the –OH and –COOH and NH2- polar groups that are presented in Arabic Gum, sodium alginate and chitosan respectively. However, at pH 7.1 (near to neutral), water tends to penetrate into the polymer chains to form hydrogen bond through –OH, –COOH, and NH2- groups and fills up the space along the chains resulting in lower swelling indices compared to acidic medium. However, inverse swelling trends were observed in the other hydrogels [11, 22].

An optimum response surface analysis results for swelling indices of 504.98 % (swelling time 29.3 minute with Arabic Gum content in the beads equals 6.4 wt.%, at 25°C), was estimated for the beads swollen at pH 3.9, compared to 207.97 % (swelling time 29.3 minute with Arabic Gum content in the beads equals 7.8 wt.%, at 50°C) for the beads swollen at pH 7.1. The acceptable regression coefficients for the swelling processes in both acidic and neutral media confirm the capability of the estimated models to explain the experimental results. The polynomial empirical model, R² (adjusted to d.f.) and the optimized values of swelling degree estimated from RSA analysis are shown in Table 3.

In conclusion; the prepared composite polymer beads are less stable in acidic medium, pH 3.9 compared to neutral medium.

Table 3. The polynomial empirical model, R² (adjusted to d.f.) and the optimized values of Swelling degree estimated from RSA analysis

| Medium | The polynomial empirical model estimated from RSA | R²  | Optimized swelling % and Conditions |
|--------|-----------------------------------------------|-----|------------------------------------|
| pH: 3.9 | Swelling % = 759.29 - 14.86 G - 2.93 T - 1.29 t - 0.0250 G² + 0.26 G T + 0.0195 GT - 0.203 T² + 0.059 Tt - 0.0106 t² | 89.98 | Optimum value = 504.98 Arabic Gum wt. % = 6.4, Temp. = 25 °C, Time = 29.3 min. |
| pH: 7.1 | Swelling % = 214.65 + 2.51 G - 1.28 T - 0.84 t - 0.059 G² - 0.32 GT + 0.0026 Gt + 0.030 T² - 0.00015 T t + 0.003 t² | 79.69 | Optimum value = 207.79 Arabic Gum wt. % = 8.7, Temp. = 50 °C, Time= 29.3 min. |
On the other hand, the experimental results of the in-vitro drug releasing from the polymer hydrogel polymer in acidic buffer solution pH (3.9) and neutral one pH (7.1) are shown in Table 4 and Table 5

Table 4. Drug releasing data from the hydrogel polymer in phosphate buffer solution pH (3.9)

| Release time (h) | Drug loading capacity (mg) versus drug release %, pH (3.9) |
|-----------------|----------------------------------------------------------|
|                 | 25  | 50  | 75  | 100 | 125 | 150 |
| 0.5             | 5.44| 9.70| 10.00|11.16|11.97|12.86|
| 2               | 14.75| 16.57| 17.14|18.84|21.83|21.43|
| 4               | 20.51| 27.91| 28.57|28.99|24.79|30.00|
| 6               | 32.71| 37.31| 38.57|39.86|40.99|42.86|
| 8               | 41.36| 46.27| 47.14|49.28|52.11|62.86|
| 10              | 52.54| 61.19| 62.86|65.22|65.35|75.71|
| 12              | 66.10| 70.15| 71.43|72.46|77.46|85.71|
| 16              | 72.88| 76.12| 77.14|81.16|87.61|89.291|
| 18              | 77.97| 82.09| 83.43|84.06|88.73|91.00|

Table 5. Drug releasing data from the hydrogel polymer in buffer solution pH (7.1)

| Release time (h) | Drug loading capacity (mg) versus drug release %, pH (7.1) |
|-----------------|----------------------------------------------------------|
|                 | 25  | 50  | 75  | 100 | 125 | 150 |
| 0.5             | 4.41| 4.48| 5.71| 5.51| 6.13| 0.00|
| 2               | 9.66| 10.45| 12.86|13.04|14.23| 7.14|
| 4               | 19.15| 20.15| 21.43|24.35|25.63|15.71|
| 6               | 28.81| 29.85| 30.29|30.77|32.96|27.14|
| 8               | 33.90| 37.01| 41.43|42.04|42.25|34.291|
| 10              | 37.29| 45.37| 47.43|50.72|52.11|44.29|
| 12              | 44.07| 49.25| 51.43|52.90|53.52|54.29|
| 16              | 52.54| 59.70| 60.43|61.01|61.97|58.57|
| 18              | 59.32| 62.69| 64.29|65.22|69.01|64.29|

The release pattern of the entrapped drug from the hydrogels of the optimized swelling index loaded with different amount of the drug (25-150 mg) are shown in Fig. 7 and Fig. 8 respectively. The release of the drug occurs owing to opening the pores of matrix network due to swelling of the hydrogel beads. It is noted that initially, throughout the first 2 h of releasing (pH 3.9), the drug release speed and the released amount from all the formulations seemed to be lesser (14.7-21.4 %) with similar trend confirming the minimal drug release in the acidic medium of stomach, the same sequence can be seen in (pH 7.1) with much lesser response in comparison. The drug release amount and speed then increased depending on the loading amount of the drug such as the release speed of the beads with high drug loading is higher than that of those with low drug loadings. However, after about 12 hours, the release reached mostly an equilibrium stage at which the major quantity of the drug (66.1-85.7 %) was released from the polymer beads in (pH 3.9), while (44-54 %) in (pH 7.1)
Figure 7. The release pattern of the entrapped drug from the hydrogel polymer (pH 3.9)

Figure 8. The release pattern of the entrapped drug from the hydrogel polymer (pH 7.1)

It's so obvious that the releasing sequence in acidic medium is much better than the neutral one, and this enhance the idea that the human body get much better advantage from an oral-intake drug in acidic medium presented by the stomach. The Morphological characterization of the optimized polymer beads loaded with drug before and after drug release were visualized using Scanning Electron Microscope (SEM) type (QUANTA 450) as shown in Fig. 9 and Fig. 10 respectively. The test was performed at the (Research Center of Soran University, Soran, Iraq).
It is well noted that, before drug release, the beads had a homogenous, intact and compact structure with denser surface (Fig. 9). Polymeric debris was seen on the beads surface due to gelling processes during beads preparation and development of polymer blend matrix. Big differences in beads morphology after drug releasing are observed (as shown in Fig. 10). The beads showed swollen behavior which explains the release profile of the drug from the beads. In addition, the beads lost their shape due to erosion and swelling activities [22, 24, 25].

4. Conclusion
Natural polymer composites based on (Sodium alginate-Chitosan-Arabic Gum) showed promising application as drug carriers and in pH-sensitive drug delivery systems. The swelling behavior and the drug release characteristics depend on the polymers formulations in the composite as well as the pH of the medium, and the amount of the loaded drug. RSM methodology is an applicable tool to model and optimize the performance of the polymer beads for medical applications. Arabic Gum content showed significant impact in the swelling process.

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