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ORIGINAL ARTICLE

Preparation and optimization of superabsorbent hydrogel micromatrices based on poly(acrylic acid), partly sodium salt-*g*-poly(ethylene oxide) for modified release of indomethacin

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Abstract

The purpose of this study was to prepare modified-release dosage of indomethacin (IND) in the form of micromatrices based on a superabsorbent hydrogel (SAH), poly(acrylic acid), partly sodium salt-*g*-poly(ethylene oxide) (PAAc-Na-*g*-PEO). A soaking procedure was used for the preparation of drug-loaded hydrogel micromatrices. The amount of IND, volume of drug-loading solution, and amount of PAAc-Na-*g*-PEO granules used for preparing micromatrices were the independent factors. The dependent factors were the measured responses from micromatrices, that is, percent recovery, percent entrapment efficiency, and the time at which 63.2% of the drug was released (T_d, minutes). A three-factor, three-level full factorial design (33) was created to optimize formulations. Nonlinear regression analysis indicated a good correlation between the measured responses and the independent factors. Optimum responses were obtained from medium levels of IND and SAH and low level of drug-loading solution. Differential scanning calorimetry, X-ray diffraction analysis, and scanning electron micrography indicated that IND crystals are physically adsorbed into the pores and irregular spaces of the hydrogel.

Key words: *Factorial design; indomethacin; modified release; pH-responsive; superabsorbent hydrogel*

Introduction

The oral route of drug delivery is the most preferred and patient-convenient means of drug administration. However, the absorption of the drug through this route can be quite erratic and inefficient because of physiological characteristics of the gastrointestinal (GI) system and physicochemical properties of a drug such as solubility and permeability. Modified-release dosage forms are designed considering the physicochemical properties of the drug and their interaction with the physiological factors; ideally, the drug is released at the predetermined rate and at the desired site within the GI system[1–5]. Modified-release dosage forms can be formulated as single-unit or multiple-unit systems. In terms of bioavailability, multiple-unit dosage forms ensure more reproducible drug absorption, more consistent blood levels, and predictable GI transit time. They spread out more uniformly in the GI tract, thus reducing the potential for gastric irritation caused by drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). They are also useful for site-specific targeting within the GI tract[2,5–9].

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids, yet they are insoluble because of the presence of physical or chemical cross-links, entanglements, or crystalline regions. The ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels makes them suitable as

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modified drug delivery systems[8,10–18]. Drug release from hydrogels generally involves simultaneous absorption of water and desorption of drug via a swelling-controlled mechanism depending on environmental stimuli such as temperature, pH, specific endogen molecules, inflammation, and so on. Among these, pH-responsive hydrogels have been most frequently used for site-specific drug delivery. pH-responsive hydrogels contain pendant acidic, that is, carboxylic and sulfonic acids, or basic, that is, ammonium salts groups. These hydrogels show changes in their equilibrium swelling behavior as a result of changing the external pH while they are glassy in their dehydrated state and, thus, regulate drug release or solute diffusion[12,19,20]. Cationic hydrogels have been employed for localized delivery of drugs in the stomach, whereas anionic hydrogels have been extensively studied to target drugs, especially peptide–protein drugs, to the small intestine and colon[8,9,16–18,21,22].

Polyelectrolytes, such as poly(acrylic acid), poly(methacrylic acid), and poly(*N*,*N*'-diethylaminoethyl methacrylate), have been widely used to prepare pH-responsive hydrogels[23]. Graft copolymers based on poly(vinyl alcohol)–poly(acrylic acid/methacrylic acid), poly(acrylic acid)–poly(ethylene oxide), and poly(methacrylic acid)–poly(ethylene oxide) were also synthesized as pH-responsive hydrogels[16,20,24]. Superabsorbent hydrogels (SAHs) are structurally cross-linked hydrophilic polymers that have the ability to absorb large amounts of water or aqueous fluids (10–1000 times their original weight or volume) in relatively short periods of time. The monomers commonly used in their synthesis are acrylamide, acrylic acid, and salts of acrylic acid including sodium and potassium acrylates. Fast swelling is based mainly on the small size of the SAHs. SAHs were introduced into agriculture and diaper industries at first and were then applied in other industries where an excellent water-holding capacity was of prime importance[25]. In our study, the SAH studied was poly(acrylic acid), partly sodium salt-*g*-poly(ethylene oxide) (PAAc-Na-*g*-PEO).

Indomethacin (IND) is a very effective anti-inflammatory and antipyretic drug with analgesic property. Serious GI toxicity such as bleeding, ulceration, and perforation can occur in patients treated chronically with NSAID therapy. IND is a poorly soluble drug. Its low solubility can increase small intestinal irritation because of the prolonged contact with the mucosa[26,27]. IND has a pH-dependent solubility profile in the pH range of the GI system. Values of 0.005, 0.030, 1.0, and 1.3 mg/mL have been reported at pH 1.0, 5.0, 6.8, and 7.4, respectively[28]. Thus, incomplete drug release in the GI system could result and must be addressed in formulation development. Numerous methods, such as prodrugs, polymeric micelles, ultrasound-aided compaction of granules containing lactose-based excipients, interactive mixtures using fine lactose, emulsions, and polymeric nanoparticles and microparticles, have been reported to improve dissolution characteristics of IND[29–37]. pH-responsive hydrogels have also been evaluated for enabling the drug delivery or release to take place preferentially in the intestine[38,39].

The objectives of this study were (i) to prepare an oral multiple-unit drug delivery system in the form of micromatrices containing IND for targeting the small intestine, (ii) to study the effect of preparative variables on the properties of the micromatrices (recovery, drug entrapment efficiency, and drug release), (iii) to optimize the formulations by a factorial design, and (iv) to characterize the micromatrices physicochemically. A SAH, PAAc-Na-*g*-PEO, was used as a matrix material, which is in free-flowing granular form with a particle size of 100–850 μm. AAc monomer and PEO linear homopolymer in the structure of the SAH are frequently used in the synthesis of different hydrogels. However, their granular polymer form, PAAc-Na-*g*-PEO, has not been studied previously for drug release.

Materials and methods

Materials

IND was kindly supplied by Nobel İlaç (İstanbul, Turkey). PAAc-Na-*g*-PEO (lot number, 13121LC) was purchased from Sigma-Aldrich (Milwaukee, WI, USA). All other chemicals and reagents were of analytical grade.

Measurement of swelling characteristics

Accurately weighed samples (0.1 g) of dry PAAc-Na-*g*-PEO granules were placed into nylon bags and immersed in beakers containing 50 mL of pH 1.2 simulated gastric fluid without enzymes, pH 3.0 phthalate buffer, and pH 4.5, 6.8, and 7.2 phosphate buffers in a shaker bath at 37°C[40]. The bags were removed at predetermined time intervals, excess water was blotted superficially, and the bags were weighed. The change in the weight was observed until a constant weight was reached for each sample (n = 3). The same procedure was performed in the samples in pH 6.8 phosphate buffer maintained at different temperatures (10°C, 25°C, 50°C, and 75°C) (n = 3). The following equation was used to calculate the weight swelling ratio:

$$\text{Swelling ratio (\%)} = \frac{w - w_0}{w_0} \times 100, \quad (1)$$

where w and w_0 are the sample weights at time t in the wet and the dry state, respectively.

Preparation of micromatrices

IND was dissolved in the mixture of pH 6.8 phosphate buffer and ethanol (1:1, v/v). Loading was accomplished by soaking dry PAAc-Na-*g*-PEO granules in the drug solution at room temperature, and the mixture was then stirred under mild agitating conditions till alcohol was removed by evaporation following the change in the volume of suspension at 50°C. Subsequently, the mixture was kept in a dark room at room temperature for 24 hours to further diffuse IND into the swollen SAH granules. The drug-loaded micromatrices were filtered and washed with pH 1.2 simulated gastric fluid, in which the drug does not dissolve, to remove unloaded drug particles. The micromatrices were dried in an oven at 50°C until a constant weight was reached and stored in a desiccator. The compositions of the formulations are given in Tables 1 and 2.

Entrapment efficiency and recovery

The drug content was determined by dispersing 100 mg of micromatrices in 100 mL chloroform and agitating with a magnetic stirrer for 3 hours to extract the drug. After the mixture was filtered and diluted with chloroform, IND concentration was determined spectrophotometrically at 242.5 nm (Shimadzu UV-1202, Tokyo, Japan) ($n = 3$). The drug entrapment efficiency was calculated as follows:

$$\text{Entrapment efficiency}\,(\%) = \frac{\text{calculated drug content}}{\text{theoretical drug content}} \times 100. \quad (2)$$

Recovery was calculated as the ratio of the amount of micromatrices obtained to the solid content used for the preparation of micromatrices, multiplied by 100.

In vitro drug-release studies

Release studies were conducted in USP Apparatus 1 (basket method) (SOTAX AT 7smart; Sotax AG, Basel, Switzerland) with three replicates, according to the USP monograph for Indomethacin Extended-Release Capsules[40]. A weighed amount of micromatrices equivalent to 25 mg IND was put into the basket. The release medium was 750 mL of pH 6.8 phosphate buffer maintained at 37°C. The basket rotation speed was maintained at 75 rpm. In all experiments, 5 mL of sample was withdrawn at determined intervals, filtered through a 45-µm membrane filter (Sartorious GmBH, Göttingen, Germany), and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were assayed by UV spectrophotometry at 263 nm. Cumulative percentages of the drug released from micromatrices were calculated. Additionally, a dissolution test according to the monograph given in USP under the title of 'Delayed-Release Dosage Forms' was performed on the formulation selected depending on the evaluated properties of the micromatrices[40].

Table 1. The levels and range of the independent factors with the assigned codes.

	Independent factors					
	Amount of IND (mg)		Volume of drug-loading solution (mL)		Amount of PAAc-Na-*g*-PEO (mg)	
Levels	X_1	Code	X_2	Code	X_3	Code
Low	375	−0.5	100	−1	750	−1
Medium	750	0	200	0	2250	0
High	1500	+1	300	+1	3750	+1

Table 2. The compositions of the studied formulations and the measured responses for 3^3 full-factorial design.

Formula	Independent factors			Measured responses		
code	X_1	X_2	X_3	Y_1	Y_2	Y_3
F1	−0.5	−1	−1	66.88	53.05	4.36
F2	−0.5	−1	0	86.01	66.46	5.58
F3	−0.5	−1	+1	90.95	72.84	4.78
F4	−0.5	0	−1	56.93	42.24	2.25
F5	−0.5	0	0	81.65	56.32	4.90
F6	−0.5	0	+1	85.64	70.72	2.81
F7	−0.5	+1	−1	50.82	11.10	3.71
F8	−0.5	+1	0	80.45	25.91	2.51
F9	−0.5	+1	+1	69.30	44.97	3.16
F10	0	−1	−1	54.44	99.02	38.48
F11	0	−1	0	83.33	88.28	6.76
F12	0	−1	+1	83.40	84.88	4.67
F13	0	0	−1	58.88	55.67	10.48
F14	0	0	0	83.22	61.33	1.00
F15	0	0	+1	83.33	60.17	5.27
F16	0	+1	−1	46.40	19.77	6.09
F17	0	+1	0	78.30	48.20	5.81
F18	0	+1	+1	83.48	48.22	4.89
F19	+1	−1	−1	41.06	46.97	20.85
F20	+1	−1	0	68.39	68.10	14.46
F21	+1	−1	+1	78.17	57.92	10.37
F22	+1	0	−1	44.91	80.96	10.26
F23	+1	0	0	73.75	75.00	7.41
F24	+1	0	+1	82.46	77.53	6.95
F25	+1	+1	−1	31.60	29.78	20.48
F26	+1	+1	0	66.24	58.12	5.45
F27	+1	+1	+1	77.75	67.73	5.63

Y_1, percent recovery; Y_2, percent entrapment efficiency; Y_3, time parameter of Weibull distribution; T_d, minutes (time at which 63.2% of the material is released).

Release data were analyzed according to Weibull distribution in linearized form with the linear regression module of SPSS 8.0 for Windows (SPSS, Chicago, IL, USA)[41] as

$$\log\left[\ln\left(\frac{1}{1-Q}\right)\right]=\beta\log T-\beta\log T_{\mathrm{d}}, \tag{3}$$

where Q is the percent dissolved at time T, β is the shape parameter, and T_{d} is the time parameter at which 63.2% of the drug is dissolved.

Scanning electron micrography

The shape and surface characteristics of micromatrices were examined by a scanning electron microscope (SEM) (JSM 6400, JEOL Ltd., Tokyo, Japan). Micromatrices were dusted onto double-sided carbon tape on an aluminum stub. The stubs were coated with gold using a cool sputter coater to a thickness of 400 Å. The samples were imaged using a 20-kV electron beam.

Powder X-ray diffractometry

Powder X-ray diffractometry (XRD) patterns were obtained with CuK_{α} radiation (0.154 nm, nickel filtered) at 35 kV and 20 mA over a 2θ range of 4°–45° after spreading IND, PAAc-Na-*g*-PEO granules, micromatrices, and physical mixture on the glass plates (Rigaku, Miniflex, Japan). Physical mixture was made by grinding the drug with the solid hydrogel.

Differential scanning calorimetry

Thermal analysis was performed on the drug, hydrogel, micromatrices, and physical mixture using a differential scanning calorimetry (DSC) (TA Instruments Q100, New Castle, DE, USA). Samples (5 mg) were accurately weighed into aluminum pans and then sealed. Thermograms were obtained at a scanning rate of 10°C/minute over a temperature range of 0°–200°C under nitrogen.

Factorial design

The amount of IND (X_1), volume of drug-loading solution (X_2), and amount of PAAc-Na-*g*-PEO granules (X_3) used for preparing micromatrices were the independent factors. The dependent factors were the measured responses from micromatrices, that is, the percent recovery (Y_1), percent entrapment efficiency (Y_2), and time parameter of Weibull distribution, T_{d} (time at which 63.2% of the material is released) (Y_3). A three-factor, three-level full factorial design (3^3) was created to elucidate the effects of independent factors on measured responses[42–44]. The levels and range of the independent factors with the assigned codes are given in Table 1. A polynomial equation was employed to quantify the effects of independent factors on the measured responses.

$$\begin{aligned}Y=&B_0+B_1X_1+B_2X_2+B_3X_3+B_{11}X_1X_1\\&+B_{22}X_2X_2+B_{33}X_3X_3+B_{12}X_1X_2\\&+B_{13}X_1X_3+B_{23}X_2X_3+B_{123}X_1X_2X_3,\end{aligned} \tag{4}$$

where Y is the measured response, X_{i} is the level of the independent factors, B_{i} represents coefficients, and B_0 is the intercept. B coefficients with their standard errors and descriptive statistics of regression for the model were calculated by the nonlinear regression module of Statistica 5.0 for Windows (Statsoft, Tulsa, OK, USA). In nonlinear regression analysis, the quasi-Newton method minimized the least squares. The compositions of the studied formulations and the measured responses are shown in Table 2.

Results and discussion

Swelling properties

The swelling property of the hydrogels determines both the conditions of drug-loading and the drug-release mechanism. The hydrogels have a porous structure. The space available between macromolecular chains is often regarded as a pore. When the hydrogel begins to absorb water, firstly the ionic, polar, and hydrophobic groups in the structure become saturated with water and then the pores are filled[13,18,25]. The influence of the pH value of the medium at 37°C on the swelling behavior of PAAc-Na-*g*-PEO granules is shown in Figure 1. Maximum swelling ratios were found to increase in a pH-dependent pattern. The lowest maximum swelling degree was observed in medium pH 1.2. At lower pH values, a complex formation results from the formation of temporary physical cross-links because of the intramolecular hydrogen bonding between PEO- and PAAc-dependent groups[20]. The maximum swelling ratio tapers off at lower pH values because of the complex being less hydrophilic. Additionally, hydrogen bonds shorten free space inside the hydrogel network and limit the mobility of the polymer chains, causing water to diffuse out of the hydrogel network. Therefore, the swelling ratio decreased in pH 1.2 medium over time. The highest maximum swelling degrees were reached at pH 6.8 and 7.2, this being due to the complete dissociation of carboxylic acid groups of acrylic acid in the structure of the hydrogel at this pH values. The pH of

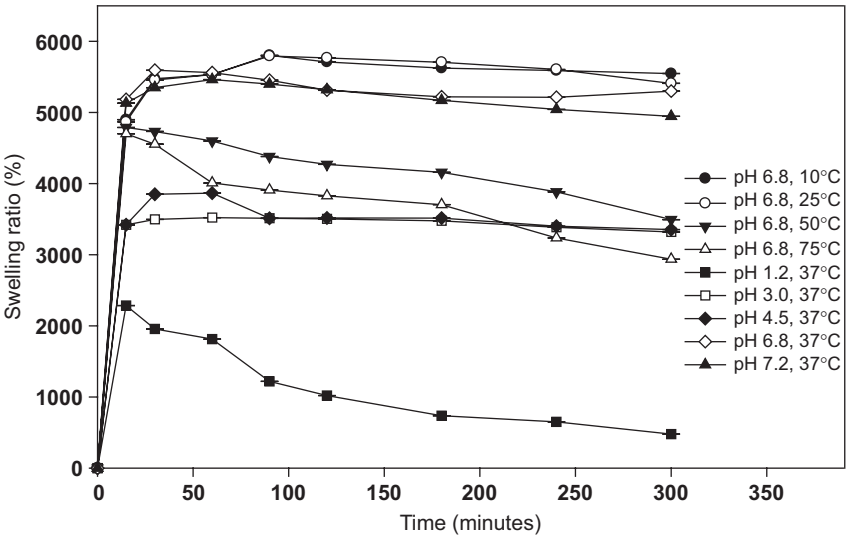

Figure 1. Effects of pH and temperature on the swelling ratios of PAAc-Na-*g*-PEO as a function of time.

PAAc-Na-*g*-PEO (1%, w/v, in 0.9% sodium chloride) is 6.0 ± 0.5. As the dissociation constant of acrylic acid is pK_a = 4.25, the consecutive maximum swelling degrees were observed around these pH values. The charged groups cause electrostatic repulsion between the polymer chains, thus resulting in relaxation of the hydrogel network and absorption of more water[16,19]. A 22–55 times increase in original weight in relatively short periods of time (30–60 minutes) indicates PAAc-Na-*g*-PEO becomes a SAH[11,25].

Experiments to determine temperature sensitivity of the hydrogel were performed in phosphate buffer solution with pH 6.8 at 10°C, 25°C, 37°C, 50°C, and 75°C. As can be seen in Figure 1, maximum swelling ratio of PAAc-Na-*g*-PEO in pH 6.8 buffer at different temperatures was also quite high. A 47–58 times increase in the weight of the hydrogel was observed over the period of 15–90 minutes at all temperatures, and the equilibrium values of swelling degree were attained at 10°C, 25°C, and 37°C. Nevertheless, PAAc-Na-*g*-PEO exhibits a continuous fall in swelling ratios at 50°C and 75°C as a function of time. This is a consequence of volume collapse upon warming. At these higher temperatures, water is excluded from the hydrogel. For the PAAc-Na-*g*-PEO hydrogel, the hydrophilic carboxylic acid groups and the oxygen atom of PEO form intermolecular hydrogen bonds with the hydrogen atom of the aqueous solution at low temperatures. The hydrogen bond formation is very temperature-dependent, and the bond is liable to break when the temperature is increased, while hydrophobic interactions are enhanced, resulting in a collapsed state for the gel and deswelling[45,46]. Thus, decreasing temperature can induce swelling.

Preparation of the micromatrices

For the preparation of drug-loaded hydrogel micromatrices, a soaking procedure was used. A good swelling degree of the hydrogel and a concentrated solution of the drug are primary requirements in this procedure. Thus, an aqueous solution of hydrophilic drugs can be loaded readily into hydrogels using this method. In the case of drugs that are too lipophilic, a cosolvent miscible with water should be used to dissolve the drug, and the available solvents for this purpose are restricted to ethanol and methanol[47].

Considering the swelling behavior of PAAc-Na-*g*-PEO in different media at different temperatures, phosphate buffer (pH 6.8) maintained at 25°C was used as drug-loading solution. The volume range of the drug-loading solution (Table 1) was determined from the swelling ratio of PAAc-Na-*g*-PEO in pH 6.8 phosphate buffer. IND is a slightly soluble drug (0.001 g/mL in pH 6.8 phosphate buffer)[28]. Ethanol was used as a cosolvent in the drug-loading solution to increase the solubility of IND and to prepare concentrated solutions. The amount of IND (X_1), volume of drug-loading solution (X_2), and amount of PAAc-Na-*g*-PEO granules (X_3) were evaluated as the preparative variables (independent factors). The preparation in the form of drug-impregnated porous hydrogel granules is referred to as micromatrices.

Optimization and evaluation of the micromatrix formulations

Percentage recovery and drug entrapment efficiency of micromatrices

The results of the nonlinear regression analysis (*B* coefficients and R^2 values) and analysis of variance (*P* values)

Table 3. Results of regression analysis and *P* values obtained from analysis of variance (ANOVA).

	Y_1 (% recovery)		Y_2 (% drug entrapment efficiency)		Y_3 (T_d, minutes)	
Factors	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
X_1	−5.402	0.0199*	17.937	0.0199*	8.002	0.0389*
X_2	−4.294	0.0002*	−17.789	<0.0001*	−2.857	0.0806
X_3	14.791	<0.0001*	8.611	0.0110*	−3.387	0.0419*
X_1X_1	−4.648	0.1489	−18.318	0.0910	−5.957	0.2706
X_2X_2	−3.587	0.0299*	−9.364	0.0793	3.634	0.1754
X_3X_3	−12.016	<0.0001*	−3.994	0.4358	3.210	0.2284
X_1X_2	2.998	0.0471*	12.159	0.0183*	−0.384	0.8735
X_1X_3	5.440	0.0013*	−2.858	0.5454	−2.494	0.3089
X_2X_3	0.610	0.5872	6.758	0.0832	2.575	0.1889
$X_1X_2X_3$	2.123	0.2315	1.289	0.8229	−1.808	0.5428
Intercept	83.155	<0.0001*	71.744	<0.0001*	4.710	0.1601
R^2**	0.9840		0.8891		0.7753	

*$P < 0.05$, significant parameters. **Determination coefficient.

are shown in Table 3. Determination coefficients (R^2 values) obtained for percent recovery and drug entrapment efficiency of the micromatrices were 0.9840 and 0.8891, respectively. These values reveal a good correlation between the dependent factors and the measured responses besides representing the performance of the polynomial equation [Equation (3)]. Coefficients with one factor describe the linear effects of the factors while the coefficients with more than one factor indicate an interaction between the factors. The coefficients of the factors squared represent the quadratic (nonlinear) nature of the relationship. Negative signs of the coefficients indicate negative quantitative (antagonistic) effect of the factor on the measured response just as positive signs indicate positive quantitative (synergistic) effect. Contribution of the factors with insignificant *P* values ($P > 0.05$) on measured responses is not important, and these factors can be considered as negligible[42–44].

The recoveries of micromatrices prepared with the formulations in Table 2 ranged between 31.60% and 90.95%. Three independent factors (X_1, amount of IND; X_2, volume of drug-loading solution; and X_3, amount of PAAc-Na-*g*-PEO) were found to be significantly effective on the percent recovery (Y_1) ($P < 0.05$) (Table 3). The levels of the drug and the drug-loading solution negatively affected the percent recovery while the level of PAAc-Na-*g*-PEO had positive effect (Table 3). The relationships between the volume of drug-loading solution and the percent recovery and between the amount of PAAc-Na-*g*-PEO and the percent recovery were quadratic. As seen in Figure 2, a lower amount of IND and higher amount of PAAc-Na-*g*-PEO in the formulations led to high recoveries of the micromatrices. Although the effect of the level of the drug-loading solution on the recovery of micromatrices

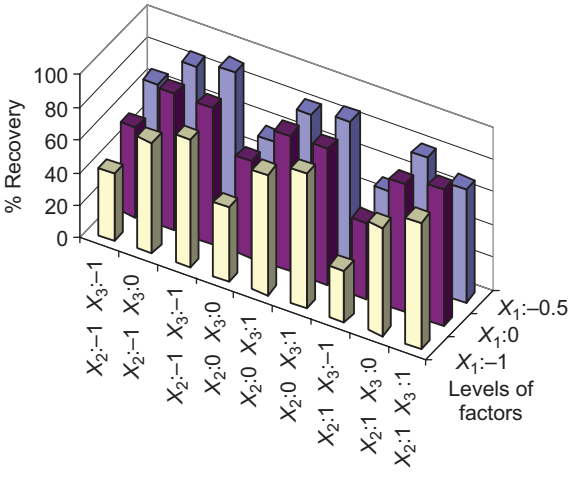

Figure 2. Effects of the amount of IND (X_1), volume of drug-loading solution (X_2), and amount of PAAc-Na-*g*-PEO granules (X_3) on the recoveries of micromatrices.

was not so clear, increasing volume of the solution resulted in decreasing percent recovery, as the hydrogel could not completely absorb the drug-loading solution and consequently IND (Table 2). The lowest values for recovery were observed for the formulations prepared with the hydrogel at low level and IND at high level (Table 2 and Figure 2). This result shows that a great amount of drug cannot be entrapped into the pores of the hydrogel and is easily removed during washing. Interactions of IND–drug-loading solution ($P = 0.0471$) and IND-PAAc-Na-*g*-PEO ($P = 0.0013$) (Table 3) were found to be statistically significant, confirming the findings above. Interaction is thought of as a lack of additivity of factor effects; that is, the effect of one factor at each level on the measured

response is not parallel with that of other factors. Lack of parallelism suggests interaction[44].

Upon contact with the drug-loading solution, the hydrogel in dehydrated state allows solution diffusion into the pores. During evaporation of the solvent, the drug recrystallizes and is entrapped in the pores. IND has a similar dissociation constant ($pK_a = 4.5$) to that of AAc in the structure of the hydrogel. Carboxylic acid groups in both IND and PAAc-Na-*g*-PEO ionize in the drug-loading solution at pH 6.8. Because the drug has a net charge that is the same as that of the hydrogel, it may be excluded from the hydrogel, causing lower percent entrapment efficiency. However, ethanol in the drug-loading solution would partly suppress the ionization and thus the repulsion between drug molecules and hydrogel. The addition of alcohol to a buffered solution of a weak electrolyte increases the solubility of unionized species by adjusting the polarity of the solvent to a more favorable value[48].

The entrapment efficiency of IND in the micromatrices varied between 11.10% and 99.02%. The higher values of % drug entrapment efficiency occurred with low level of drug-loading solution and medium level of IND as 99.02%, 88.28%, and 84.88% for the micromatrices prepared from the formulations of F10, F11, and F12 (Tables 1 and 2 and Figure 3). This can be explained by complete absorption of the solution by the hydrogel without any loss of the drug to be loaded into micromatrices. The lower values of entrapment efficiency were observed with high level of the drug-loading solution, indicating that IND preferentially remained in the solution and was removed during washing and recovery (Table 2 and Figure 3). In this case, the drug amount and thus drug concentration decreases, and electric repulsion might have a more clear effect on the drug entrapment into the pores of the hydrogel. Increasing amounts of PAAc-Na-*g*-PEO did not noticeably affect the % drug entrapment efficiency in case of lower volume of drug-loading solution but increased it significantly in case of higher volume of drug-loading solution (Table 2 and Figure 3).

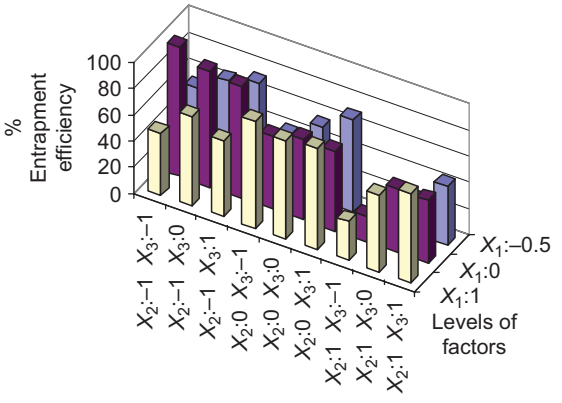

Figure 3. Effects of the amount of IND (X_1), volume of drug-loading solution (X_2), and amount of PAAc-Na-*g*-PEO granules (X_3) on the entrapment efficiency of drug in micromatrices.

Consequently, the effects of the three evaluated factors—amount of IND (X_1), volume of drug-loading solution (X_2), and amount of PAAc-Na-*g*-PEO granules (X_3)—on the % drug entrapment efficiency (Y_2) were found to be statistically significant ($P < 0.05$); the volume of drug-loading solution negatively affected the measured response while the amounts of IND and PAAc-Na-*g*-PEO demonstrated positive effect (Table 3). A significant interaction between the IND–drug-loading solution ($P = 0.0183$) was observed (Table 3).

Drug release from the micromatrices

Drug release from the hydrogels involves simultaneous absorption of water and desorption of drug via a swelling-controlled mechanism. Such swelling and diffusion cannot be described with a Fickian diffusion[12]. Release data have been applied to various kinetic models for predicting release mechanisms. The preferred model in our study was Weibull distribution with its parameters describing the types of dissolution profiles, β, and dissolution time, T_d. The shape parameter, β, characterizes the profile as either exponential ($\beta = 1$), S-shaped with upward curvature followed by a turning point ($\beta > 1$), or as one with steeper initial slope then consistent with the exponential ($\beta < 1$). The time parameter, T_d, represents the time interval necessary to dissolve 63.2% of the drug[41].

The release data of the formulations (F1–F27) were fitted to Weibull model and determined model parameters. All the formulations well fitted to Weibull model according to the regression parameters such as determination coefficients (R^2 = 0.860–0.995) and residual mean squares (RMS = 0.001–0.005). The shape parameters of dissolution profiles (β) ranged from 0.360 to 1.071, indicating that a rapid initial drug release was followed by a slow drug-release phase, as seen in Figures 4–6. A complete release of IND from all formulations except F10 was reached in 30–180 minutes. Discrepancies between the formulations were observed especially for initial release. Therefore, the release data were evaluated on the basis of T_d values (Figure 7). IND was released rapidly from formulations F1–F9 containing drug at low level (X_1: –0.5); T_d values were between 2.25 and 5.58 minutes (Table 2 and Figures 4 and 7). The rapid release of IND from these formulations was independent of the levels of other preparative variables, namely the volume of drug-loading solution (X_2) and amount of PAAc-Na-*g*-PEO (X_3). A relatively extended release was observed for the formulations containing drug at medium level (X_1: 0) and high level (X_1: +1) when compared to the formulations containing drug at low level (Figures 5–7). T_d values for these formulations

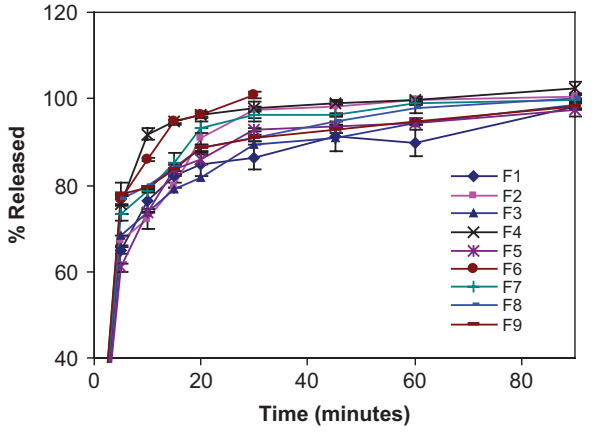

Figure 4. IND release from the micromatrices prepared with the drug at low level. The ordinate is scaled beyond the release value of 40% due to overlapping.

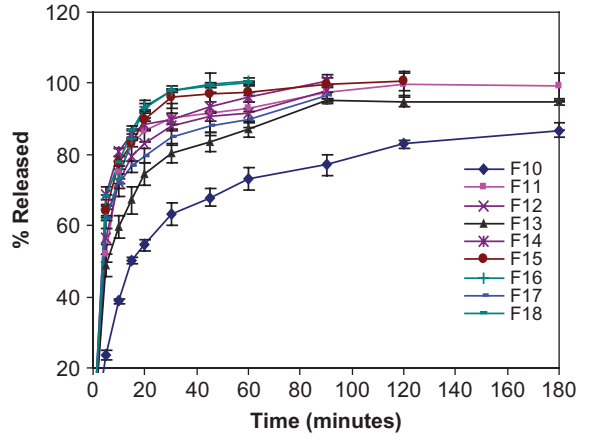

Figure 5. IND release from the micromatrices prepared with the drug at medium level. The ordinate is scaled beyond the release value of 20% due to overlapping.

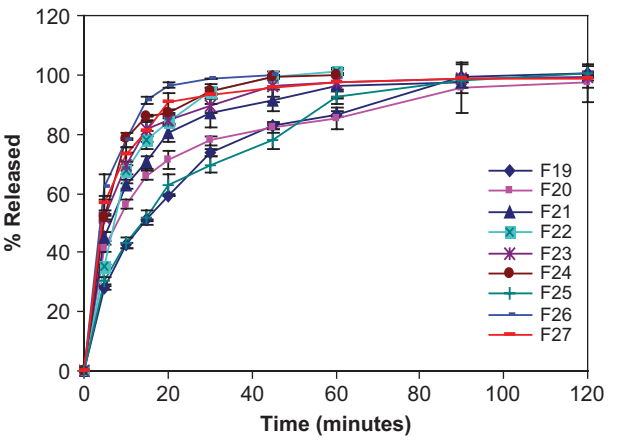

Figure 6. IND release from the micromatrices prepared with the drug at high level.

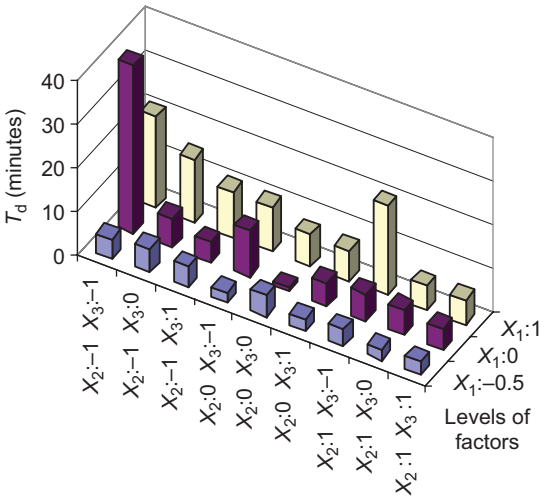

Figure 7. The time parameter, T_d, as a function of the amount of IND (X_1), volume of drug-loading solution (X_2), and amount of PAAc-Na-*g*-PEO granules (X_3).

increased especially with low level of PAAc-Na-*g*-PEO (X_3) and release time of IND was extended (Table 2 and Figure 7). Among these, F10 (X_1: 0, X_2: –1, X_3: –1) and F19 (X_1: +1, X_2: –1, X_3: –1) formulations showed the highest T_d values as 38.48 and 20.85 minutes, respectively (Table 2 and Figure 7).

According to the results of the nonlinear regression analysis, the determination coefficient (R^2 value) obtained for T_d values was 0.7753. The amount of IND (X_1) and amount of PAAc-Na-*g*-PEO (X_3) were found to be significantly effective on the T_d values (Y_3) ($P < 0.05$) (Table 3). Increasing level of IND had a positive effect on T_d values just as increasing level of PAAc-Na-*g*-PEO had a negative effect (Table 3). These results agreed well with the above findings.

The drug-release data revealed that despite the poor solubility of IND, the multiparticulate system in the form of micromatrices increases the dissolution rate of the drug. The drug release is faster through a highly porous matrix due to the area per unit of mass originated by pores. Additionally, the fast swelling of the SAH micromatrices in the release media leads to a fast desorption of the drug in the absence of significant hydrogel–drug interaction. A problem with pure drug is the aggregation of the drug crystals, thus resulting in incomplete dissolution of the drug[26,49]. It is thought that the drug is dispersed homogeneously in the form of individual crystals in the micromatrices and is easily dissolved. The slower release of IND from the micromatrices in the case of high level of drug and low level of hydrogel confirms this result.

Physicochemical characterization of micromatrices

The formulation representing the best balance of the evaluated properties (measured responses) was number 11 prepared with medium levels of IND and PAAc-Na-*g*-PEO and low level of drug-loading solution (Table 2). Formulation 11 was further evaluated for morphology, interaction between drug and PAAc-Na-*g*-PEO hydrogel, and drug-release characteristic.

The shape and surface characteristics of micromatrices prepared from formulation 11 are shown in Figure 8a–c. The micromatrices are in the form of irregular-shaped particles ranging in size from 500 to 1000 μm (Figure 8a). The surfaces of the micromatrices were porous in appearance including IND crystals (Figure 8b and c). The XRD patterns of micromatrices were examined and compared with those of the pure drug, hydrogel, and its physical mixture (Figure 9). The crystallinity of IND was clearly demonstrated by its XRD pattern shown in Figure 8c. In Figure 9d, the absence of diffraction peaks indicated the amorphous structure of the PAAc-Na-*g*-PEO hydrogel. The sharp diffraction peaks corresponding to IND were still present in the XRD patterns of the physical mixture of formulation 11 (Figure 9b). Hence, it can be concluded that the drug is found in crystalline state. The XRD pattern of the micromatrices has peaks of low density and an irregular baseline indicating typical peaks of IND, but the profile is not as sharp as with the pure drug. This emphasizes that the crystallinity of the drug is maintained in the micromatrices, at least partially, and that in these conditions the drug cannot dissolve in the hydrogel (Figure 9a)[32]. Nevertheless, a new sharp diffraction peak was observed at $\theta = 32°$ in the XRD pattern of micromatrices (Figure 9a). This peak can arise from the hydrogen bond forming between the carboxylic acid groups in both IND and PAAc-Na-*g*-PEO.

DSC was used to examine the thermal behavior of IND and formulation. Thermograms of pure drug and PAAc-Na-*g*-PEO hydrogel are presented in Figure 10–1a and b. A sharp endothermic peak corresponding to the melting point of crystalline drug was found at 161.67°C (Figure 10–1a). As seen in Figure 10–1b for PAAc-Na-*g*-PEO hydrogel, the thermal transition at 79.31°C was attributed to the glass transition temperature (T_g). The thermogram of micromatrices showed the same endothermic peak at 155.17°C with some depression in the melting of crystalline drug that might have resulted from hydrogen bonding (Figure 10–2c). The same endothermic peak was also seen at 161.39°C in the thermogram of the physical mixture (Figure 10–3d). The transitions at 74.63°C and 76.99°C in Figure 10–2c and 3d corresponded to the T_g values of hydrogel. The results of these studies indicate that IND crystals are physically adsorbed into the pores and irregular spaces of the hydrogel without presenting significant hydrogel–drug interaction.

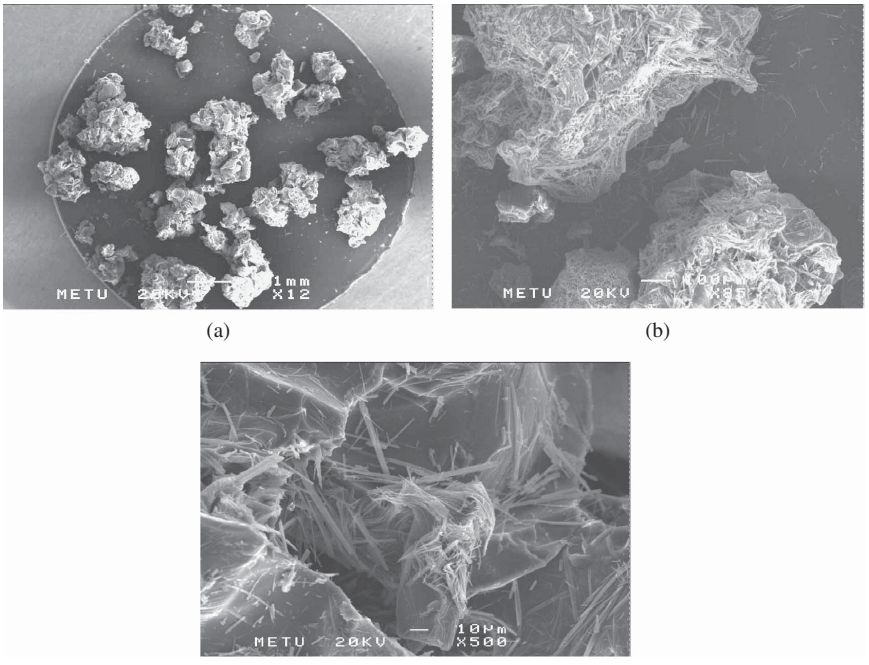

Figure 8. Scanning electron micrographs of micromatrices prepared from formulation 11 magnified by factors of 12 (a), 85 (b), and 500 (c).

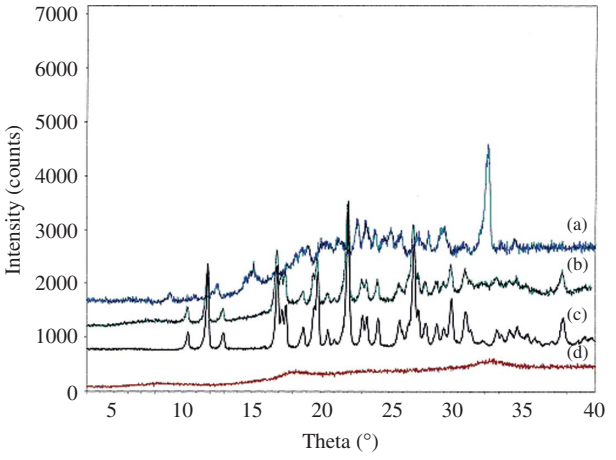

Figure 9. Powder XRD patterns of (a) micromatrices of formulation 11; (b) physical mixture of formulation 11; (c) pure drug; and (d) hydrogel, PAAc-Na-*g*-PEO.

The drug-release behavior of micromatrices prepared from formulation 11 was also examined according to the monograph titled 'Delayed-Release Dosage Forms' in USP[40]. As seen in Figure 11, 8.52% of the drug was released in simulated gastric juice (pH 1.2) in 2 hours and the amount of the drug released reached approximately 90% in phosphate buffer (pH 6.8) within 15 minutes. USP 31 states that the amount of the drug released should not exceed 10% at acid stage. Therefore, the drug-loaded micromatrices of the PAAc-Na-*g*-PEO hydrogel would be an alternative form to the delayed-release dosage forms.

Conclusions

A multiparticulate modified-release system in the form of micromatrices was prepared by soaking method using a SAH, PAAc-Na-*g*-PEO. Factorial design and nonlinear regression analysis of the results adequately described the effects of the preparative variables on the properties of micromatrices. The release of IND from the micromatrices in simulated intestinal fluid was quite rapid (i.e., 100% drug release occurred between 30 and 180 minutes) depending on the formulation employed. Producing modified release such as extended or delayed release of poorly soluble drugs like IND is not difficult, but the problem is to realize a complete release of the drug from the dosage form during its transit within the GI tract as stated by Di Colo et al.[14]. Furthermore, the low solubility of IND may increase small intestinal irritation because of the prolonged contact with the mucosa. Therefore, this release system based on a pH-responsive SAH would lead to

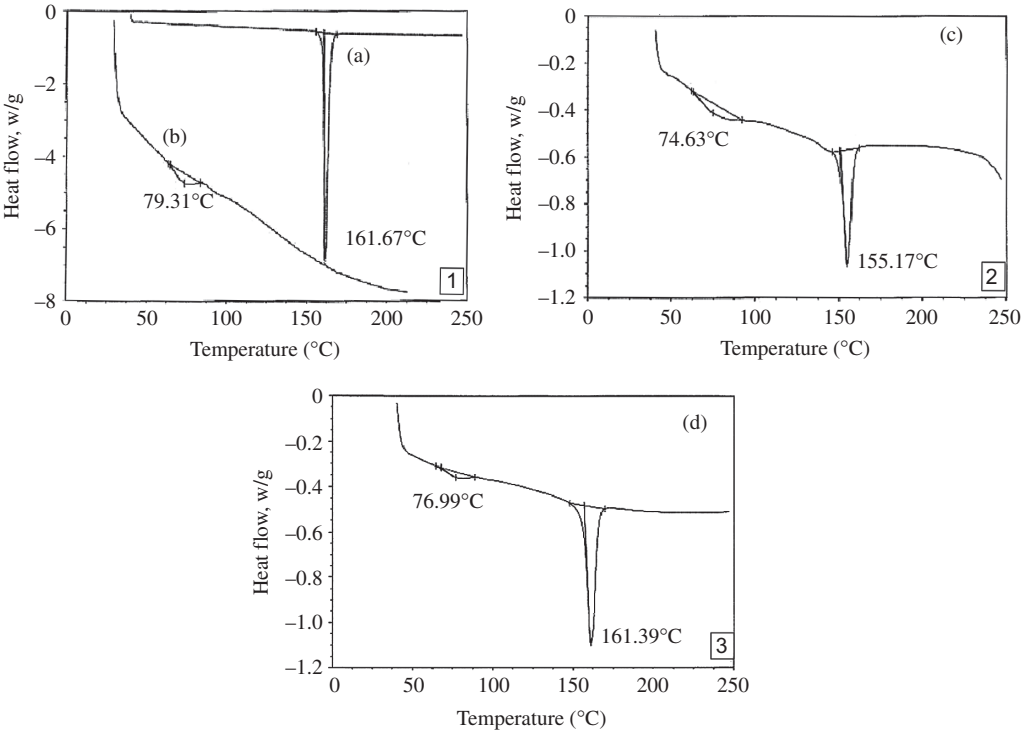

Figure 10. DSC thermograms of (a) pure drug; (b) hydrogel, PAAc-Na-*g*-PEO; (c) micromatrices of formulation 11; and (d) physical mixture of formulation 11.

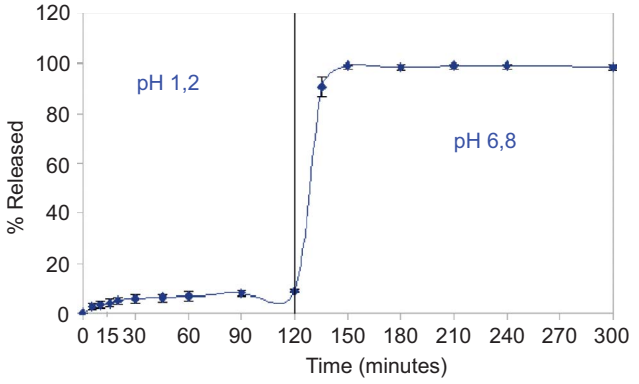

Figure 11. Delayed-release profile of IND from the micromatrices of formulation 11.

successful application of site-specific drug delivery in the GI system. Additionally, micromatrices in the form of drug-loaded particles would present the advantages of multiparticulate systems.

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