European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 804–812

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Modulation of buspirone HCl release from hypromellose matrices using chitosan succinate: Implications for pH-independent release

Hatim S. AlKhatib [a,*], Khaled M. Aiedeh [a], Yasser Bustanji [a], Saja Hamed [b], M.K. Mohammad [a], Bashar AlKhalidi [a], Samer Najjar [c]

[a] Faculty of Pharmacy, University of Jordan, Amman, Jordan
[b] Faculty of Allied Health Sciences, The Hashemite University, Zarqa, Jordan
[c] Sana Pharmaceutical Research Co., Amman, Jordan

ARTICLE INFO

Article history:
Received 8 January 2008
Accepted in revised form 18 June 2008
Available online 26 June 2008

Keywords:
Chitosan succinate
Buspirone HCl
HPMC tablets
Dialysis studies
pH-Independent release
Complex formation
Dissolution similarity

ABSTRACT

Chitosan succinate (CS) was synthesized through the acylation of chitosan with succinic anhydride. The interaction of CS with buspirone HCl (BUSP) was evaluated using dialysis experiments and shown to result in complex with a stability constant of 2.26 mM and a capacity of 0.0362 μmol BUSP/mg CS.
The extent of complexation upon dry and wet mixing of CS and BUSP was determined quantitatively using differential scanning calorimetry. The extent of the interaction was highest in wet mixtures and was found to be dependent on the pH of the granulation liquid.
CS was incorporated in BUSP-containing hypromellose (HPMC) tablets using dry mixing and wet granulation with BUSP. Tablet dissolution was tested in 0.1 N HCl and phosphate buffer, pH 6.8. According to f_2 and mean dissolution time results, the similarity of profiles increased as CS content increased with the highest f_2 value observed when CS was wet granulated with BUSP.
Dissolution was also tested in deionized water and 5% NaCl; where increased ionic strength resulted in faster dissolution suggesting an ion exchange involvement in drug release.
CS was proved effective in modulating BUSP release from HPMC matrices for pH-independent release through ionic complex formation.

1. Introduction

Formulation of a drug in matrix tablets represents an attractive approach for achieving controlled release. It offers the advantages of low cost, simple processing, limited risk of dose dumping and flexibility in terms of the range of release profiles attainable [1].

A wide range of materials for the preparation of controlled release monolithic matrix tablets are available. Hydroxypropyl methylcellulose (HPMC) is one of the most commonly used because of its hydrophilic gel-forming property, non-toxicity, cost effectiveness and wide pharmaceutical applicability [2–4].

The main mechanism by which HPMC retards drug release is by rapidly forming a gel layer at the surface exposed to aqueous fluids. The drug then dissolves into the permeating aqueous medium and diffuses from the system along the water-filled pores and capillaries [3,5]. As such, the release properties of drugs from HPMC matrices are expected to be significantly affected by its solubility in the dissolution medium [6–8]. Many drugs being weak acids, bases or salts thereof demonstrate a pH-dependent solubility and, consequently, dissolution from HPMC matrices.

As the pH of the gastrointestinal tract (GIT) varies by location, food intake, age and health of the patient, it can be expected that the *in vivo* drug release and the bioavailability of the drug would change [6].

For such drugs, it is of great importance to achieve a pH-independent release to ensure consistent release irrespective of the physiological pH and to minimize intra- and inter-patient variability in bioavailability.

To arrive at such a system, researchers [9–11] attempted to incorporate enteric polymers in the tablet matrix as pH-dependent soluble fillers. At lower pH values, enteric polymers are part of the core matrix. In contrast, at higher pH values enteric polymers dissolve and form pores and accelerate the release of weakly basic active ingredients.

Similarly, others used polymers that dissolve in acidic media but insoluble at higher pH values (e.g. Eudragit® E) to play a similar role in achieving a pH-independent release of weakly acidic drugs [12].

The use of ionizable polymers to achieve a pH-independent drug release of weak electrolytes carries with it a potential for interaction between the anionic and cationic functionalities. This type of interaction has been documented for Eudragit® [10,12–14], Carbopol®

* Corresponding author. Faculty of Pharmacy, University of Jordan, Queen Rania Street, Amman 11942, Jordan. Tel.: +962 6 5355000x23335; fax: +962 6 5339649.
E-mail address: h.khatib@ju.edu.jo (H.S. AlKhatib).

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doi:10.1016/j.ejpb.2008.06.017

[15,16], carrageenan [17–20], alginic acid [19] and carboxymethyl cellulose [10,13,19,21]. In such cases, the dissolution is influenced by the dissociation of complex formed between the drug and the ionized polymeric excipient, in addition to the usual matrix gelling and erosion and drug dissolution and diffusion.

Chitosan, which is partially deacetylated chitin (poly-β-(1 → 4)-2-acetamido-2-deoxy-D-glucopyranose), and its various semisynthetic derivatives have recently attracted great attention due to its natural origin, low cost, abundance, biocompatibility and extremely low toxicity. The reactivity of chitosan's primary amine groups allows for the preparation of a variety of derivatives with different physicochemical properties leading to different modes of interaction with drugs, excipients and biological components.

These derivatives have been evaluated as enteric coating materials [22], dissolution and absorption enhancers [23–26], controlled release matrices, colonic delivery carriers and mucoadhesive excipients [27,28].

Chitosan succinate (CS) is an anionic chitosan derivative prepared in our laboratory through the acylation of the chitosan's amino group using succinic anhydride [22,24,29,30]. The resultant derivative has a completely different solubility profile and enteric dissolution properties [22]. It has been recently used by another research group in the preparation of microspheres for improving oral bioavailability of insulin [31].

In this study, we attempted to utilize this new enteric chitosan derivative to achieve a pH-independent release profile of the weakly basic drug Buspirone from HPMC matrices. We evaluated the potential interaction between the drug and polymer and the effect of the method of incorporation of the CS on BUSP release.

2. Materials and methods

2.1. Materials

Buspirone HCl (BUSP) ($C_{21}H_{31}N_5O_2$·HCl, molecular weight 421.96) was donated by JPM Pharmaceuticals (Naor, Jordan), Metolose SR (HPMC, SEPPIC, France) was donated by JOSWE Pharmaceuticals (Naor, Jordan), chitosan (75–85% deacetylated, medium molecular weight, viscosity of 200–800 cP, 1% in 1% acetic acid, Brookfield) was purchased from Aldrich Chemical Company (St. Louis, MO, USA), lactose was purchased from Fluka (Switzerland), colloidal silicone dioxide (Aerosil 200) and magnesium stearate were purchased from Merck (Germany).

Reagent grade chemicals were purchased and used as received: sodium hydroxide (Lonover House, UK), succinic anhydride (Aldrich Chemical Company, USA) and potassium dihydrogen orthophosphate (Rasayan, India).

All solvents used (acetone, ethanol, diethyl ether, pyridine and hydrochloric acid) were of analytical grade and purchased from the Gainland Chemical Company (UK), they were used as received without further purification.

2.2. Methods

2.2.1. Synthesis of chitosan succinate

CS was synthesized as described earlier [29] with slight modification. Chitosan (30 g, 186 mmol of monomeric units) was dissolved in 1.5 L of 0.37% HCl aqueous solutions at ambient temperature and a solution of succinic anhydride (18.76 gm, 187.5 mmol) in 1.5 L of pyridine was added dropwise with vigorous stirring. The reaction pH was maintained at pH 7 by dropwise addition of 1.0 M NaOH solution which continued until the pH was stabilized. Crude product was precipitated by acetone and collected by filtration; it was then washed with acetone and diethyl ether and dried overnight at room temperature.

2.2.2. Drug–polymer interaction studies

The interaction of CS with BUSP was studied in water at 37 °C by using the method described in the literature [17]. Dialysis bags with a molecular weight cut off of 14,000 (Membra-Cel MD 44-14, Viskase Companies Inc., Darien, IL) were filled with 10 mL of a 0.1 g% w/v CS solution. The bags were closed and placed in 90 mL of BUSP solution under agitation at 37 °C until equilibrium was established (24 h).

Initial BUSP concentrations outside the dialysis bags ranging between 9 and 210 mg% w/v were used in the study.

The dialysis membrane did not allow the polymer to get out, but allowed the drug to diffuse into and eventually to interact with the polymer. After the equilibrium was established, the final drug concentration outside the dialysis bag was determined spectrophotometrically at 239 nm wavelength (Spectroscan® 80D, Spectroscan, USA).

The data were interpreted according to the following equation [17,32]:

$$r = \frac{nx}{k_d + x}, \quad (1)$$

where r is the amount of drug bound (μmol/mg of polymer) at equilibrium; x, concentration of drug unbound (mM) at equilibrium; K_d, constant of dissociation (mM); and n, maximum binding capacity of the polymer for the drug (μmol/mg of polymer).

2.2.3. Differential scanning calorimetry studies

The thermal behaviors of CS, BUSP, physical mixture (1:1 weight ratio) and wet granulated mixtures (1:1 weight ratio) prepared using 0.1 N HCl, phosphate buffer pH 7, or 0.1 N NaOH as granulating liquid and dried overnight under ambient conditions were evaluated using a Mettler Toledo DSC 823 (Mettler, Switzerland).

Samples (4–5 mg) were weighed and sealed into aluminum pans with pierced lids. The samples were heated from 25 to 250 °C at a heating rate of 10 °C/min under nitrogen purge (80 ml/min).

2.2.4. Infra-red spectrophotometric studies

Fourier-transformed infrared (FT-IR) spectra of the samples (Section 2.2.3) were obtained using the KBr disk method. A 2 mg sample of the material was mixed with potassium bromide and scanned using SHIMADZU FT-IR 8400S from 4000 to 500 cm^{-1}.

2.2.5. Formulation of BUSP tablets

Controlled release HPMC-based matrix tablets, each containing 20 mg of BUSP, were prepared by direct compression. Different formulations were prepared to evaluate the effect of the content and method of incorporation of CS on the drug release properties of the matrices.

The tablets were prepared by passing BUSP, CS, Aerosil®, HPMC and lactose through a #25 mesh sieve (710 μm) followed by manual mixing in a plastic bag for 20 min. Afterwards, sieved Mg stearate was added and mixed for an additional 2 min. Accurately weighed 300 mg portions from the above mixtures were compressed using 9 mm round-shaped flat punches in a hydraulic press (Karl Kolb, Germany) using a compression force of 10 kN for 10 s.

In one set of formulations labeled *Physical Mixture* (PM), CS was added as a dry powder to the rest of excipients to be compressed while in a second set of formulations, labeled *Wet Granulated* (WG), BUSP and CS were mixed together and granulated with a small quantity of deionized water to prepare a paste. The paste was dried overnight under ambient conditions, milled in a porcelain mortar and then passed through a #25 mesh sieve.

The resulting granules were incorporated with the rest of the tablet components to produce tablets as per the above described procedure.

Different PM and WG formulations contained three different levels of CS. The composition of the formulations evaluated is presented in Table 1.

An additional formula that does not contain CS was prepared using the same procedure as above for purposes of comparison and labeled (REF).

Approximately 20 tablets of each formulation were prepared and used and stored in glass bottles for further testing. The resultant tablets had a hardness of about 10kp and a thickness of about 4.7 mm.

2.2.6. Drug release and solubility studies

Dissolution studies were conducted in triplicates using Type II USP dissolution apparatus (Erweka DT600, Germany) over a 12-h period in 900 mL of water, 0.1 N HCl, USP phosphate buffer, pH 6.8, and 5 g% NaCl solution (ionic strength 0.86). The stirring rate and temperature were adjusted to 100 rpm and 37 ± 0.5 °C, respectively.

At predetermined time intervals, 5 mL samples were withdrawn for analysis and immediately replaced with an equal volume of fresh medium maintained at the same temperature. Samples were filtered using 0.45 μm syringe filters before the absorbance of BUSP was measured at 239 nm (SpectroScan® 80D, SpectroScan, USA). BUSP concentration was calculated from linear calibration plots. The dissolution test for each formula was performed in triplicates and the mean values as well as standard deviations were calculated.

In addition, the solubility of BUSP in the acid and buffer media was evaluated by adding excess BUSP to 5 mLs of USP phosphate buffer, pH 6.8, or 0.1 N HCl in screw cap test tubes. The contents were shaken in a DAIKI DK-SI010 shaking incubator for 24 h at 37 °C. Samples were withdrawn, filtered through 0.45 μm filter and suitably diluted and analyzed spectrophotometrically at 239 nm. All experiments were conducted in triplicate.

2.2.7. Release kinetics

Dissolution profiles were compared using the similarity factor (f_2), presented in Eq. (2), which is a logarithmic transformation of the sum squared error.

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

The f_2 statistic takes the average sum of squares of the difference between the test and reference profiles and fits the results between 0 and 100. The similarity factor is 100 when the test and reference are identical and approaches zero as the dissimilarity increases [33,34].

In addition, the kinetics of BUSP release from the various formulas was analyzed using the Peppas–Korsmeyer model [3] given in Eq. (3):

$$\frac{M_t}{M_\infty} = kt^n, \quad (3)$$

where M_t/M_∞ is the fraction of drug released at time t, k is the apparent release rate constant that incorporates the structural and geometric characteristics of the drug delivery system and n is the diffusional exponent which characterizes the transport mechanism of the drug.

In order to compare the release profile of different formulas with possible difference in release mechanisms (n values), a mean dissolution time (MDT) [12] was calculated using Eq. (4).

$$\mathrm{MDT} = \frac{n}{(n+1)(K^{(1/n)})} \quad (4)$$

The % difference between the MDT values of a single formula in 0.1 N HCl and phosphate buffer was calculated using Eq. (5).

$$\%\ \mathrm{Difference} = \left(\frac{\mathrm{MDT_{Buffer}} - \mathrm{MDT_{Acid}}}{\mathrm{MDT_{Buffer}}} \right) \times 100\% \quad (5)$$

Another form of Eq. (5) was used in evaluating the effect of the ionic strength of the dissolution medium on MDT:

$$\%\ \mathrm{Difference} = \left(\frac{\mathrm{MDT_{Water}} - \mathrm{MDT_{5\%NaCl}}}{\mathrm{MDT_{Water}}} \right) \times 100\% \quad (6)$$

Table 1
Composition of HPMC matrix tablets

Formula code	WG01	WG02	WG03	Reference (REF)
	PM01	PM02	PM03	
Component	mg/300 mg Tablet			
BUSP	20	20	20	20
HPMC	205	200	190	210
CS	5	10	20	–
Lactose	64	64	64	64
Aerosil®	3	3	3	3
Mg stearate	3	3	3	3

3. Results and discussion

3.1. Synthesis of chitosan succinate

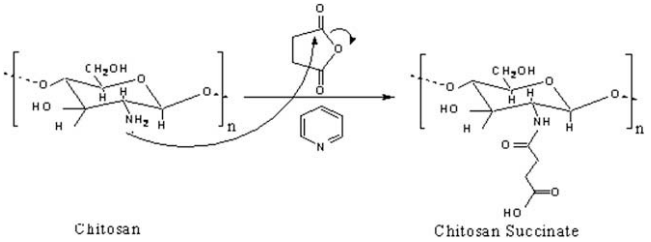
The conjugation reactions were carried out utilizing succinic anhydride in presence of pyridine [29]. Succinic anhydride is a strong electrophile that readily reacts with the nucleophilic amine groups of chitosan. Furthermore, pyridine was added as an acylation catalyst for reaction completion [35].

The selective acylation of the amine groups is probably due to their superior nucleophilic character in comparison to the surrounding hydroxyl groups (Scheme 1.).

3.2. Drug–polymer interaction studies

The linearized form of the interaction isotherm in deionized water at 37 °C is presented in Fig. 1. The properties of the interaction between BUSP and CS can be obtained easily from the data fitted to the linearized form of the equation, the interaction was found to have a stability constant of 2.001 mM (SD = 0.766) and a binding capacity of 0.0020 μmol of BUSP per 1 mg of CS (SD = 0.008).

The binding constant values of the BUSP–CS complex appear to be intermediate in comparison to that of tetrahydrozoline with hyalouronic acid (93.25 mM) and polyacrylic acid (33.81 mM) [32] and diltiazem with lambda carrageenan (0.74 mM) [17], where the complexes formed were used successfully to modulate drug release.



Scheme 1. Synthesis scheme of chitosan succinate.

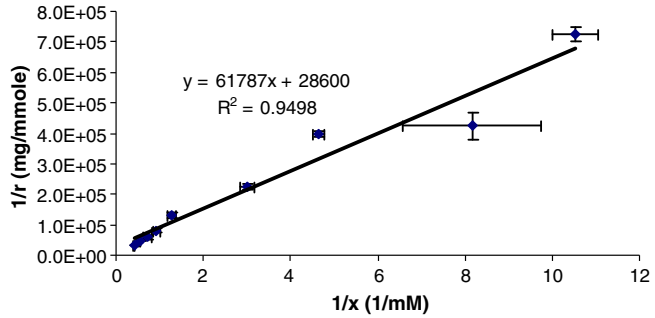


Fig. 1. Linearized form of the interaction isotherm between CS and BUSP.

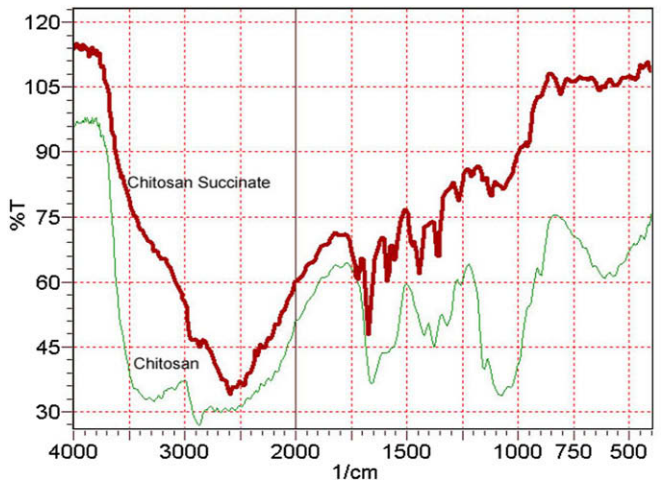


Fig. 2. IR spectra of chitosan and CS.

On the other hand, the binding capacity of BUSP–CS complex appear to be limited in comparison to the abovementioned complexes, where tetrahydrozoline with hyalouronic acid showed a binding capacity of 16.9 μmol/mg polymer, tetrahydrozoline with polyacrylic acid 11.2 μmol/mg polymer and diltiazem with lambda carrageenan 3.71 μmol/mg polymer [17,32]. This can be explained considering the limited availability of carboxylic acid groups on CS which has a degree of acid substitution of about 12% of the available amine groups [22].

3.3. Infra-red spectrophotometric studies

The IR spectra of chitosan and the prepared CS are shown in Fig. 2. The amide carbonyl stretching vibration appears in the range of 1650-1670 cm^{-1}, while the carboxylic carbonyl stretching vibration appears in the range of 1710–1735 cm^{-1}. Both observations indicate the formation of the amide bond with the succinate moiety.

3.4. Differential scanning calorimetry studies

The DSC thermograms of different samples of BUSP and CS (Fig. 3) have shown a significant change in the heat of fusion of BUSP when incorporated with CS by physical mixing and wet granulation. In addition, the wet granulated samples have shown a change in the heat of fusion depending on the pH of the granulating liquid.

The heat of fusion for the BUSP was found to be 97.3 mJ/mg; on the other hand, the heat of fusion of the 1:1 physical mixture of BUSP and CS was 91.5 mJ/mg. The difference may be due to the complex formation between BUSP and CS leading to a decrease in the amount of free solid BUSP.

On the other hand, by wet granulating BUSP with CS, the extent of interaction appears to increase resulting in a decrease in the heat of fusion of free BUSP.

Such interaction is expected to be dependent on the pH of the granulating liquid; thus wet granulation was performed using aqueous solutions with different pH values. By comparing the heats of fusion of the different wet granulated samples, it was found that the values were as follows: 81.5, 76.3, 50.8 and 28 mJ/mg for samples granulated with 0.1 N HCl, deionized water, phosphate buffer, pH 7, and 0.1 N NaOH, respectively. This could translate to percentage of uncomplexed BUSP of 83.7%, 78.4%, 52.2% and 28.8%, respectively.

The decrease in the heats of fusion of BUSP in the mixtures is consistent with the increase in the pH of the granulating liquid leading to an increase in the extent of ionization of the succinate moieties, thus supporting the ionic nature of interaction between BUSP and CS.

3.5. Dissolution studies

3.5.1. Effect of pH on the drug release

Figs. 4 and 5 show the release profiles of the different formulations containing BUSP in 0.1 N HCl and USP phosphate buffer, pH 6.8.

In general, tablets behaved as a typical HPMC-based system as they gelled gradually upon exposure to water, erosion of the tablets was dependent on the content of CS with formulas containing more CS showing a more significant erosion; however, the erosion did not result in a complete breakdown of the tablet structure and ghost matrices were always present at the end of the testing.

The dissolution results show that the drug release is faster in the acidic medium in comparison to the pH 6.8 buffer, this is expected considering the higher solubility of BUSP at lower pH values evident from the solubility values of 7.306 ± 0.178 g/mL in 0.1 N HCl and 5.602 ± 0.360 g/mL (Average ± Standard Deviation of a triplicate).

However, it is evident that the drug release profiles of the same formula in the two media become closer to each other as the content of CS increases.

This conclusion is supported by the use of the f_2 statistic with the lowest f_2 value (43.3) obtained with the REF formula not containing any CS and increasing to 46.02, 50.21 and 57.34 for the formulas PM01, PM02 and PM03.

The incorporation of CS by wet granulation with BUSP increases the efficacy of CS in achieving a pH-independent release; this is

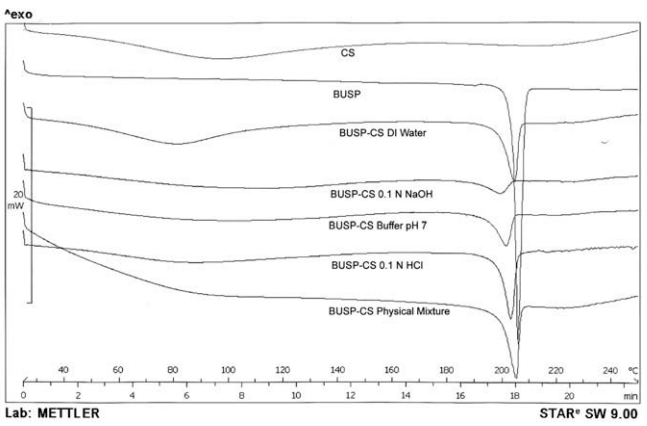


Fig. 3. DSC curves of CS and BUSP, wet granulated mixtures and dry mixture.

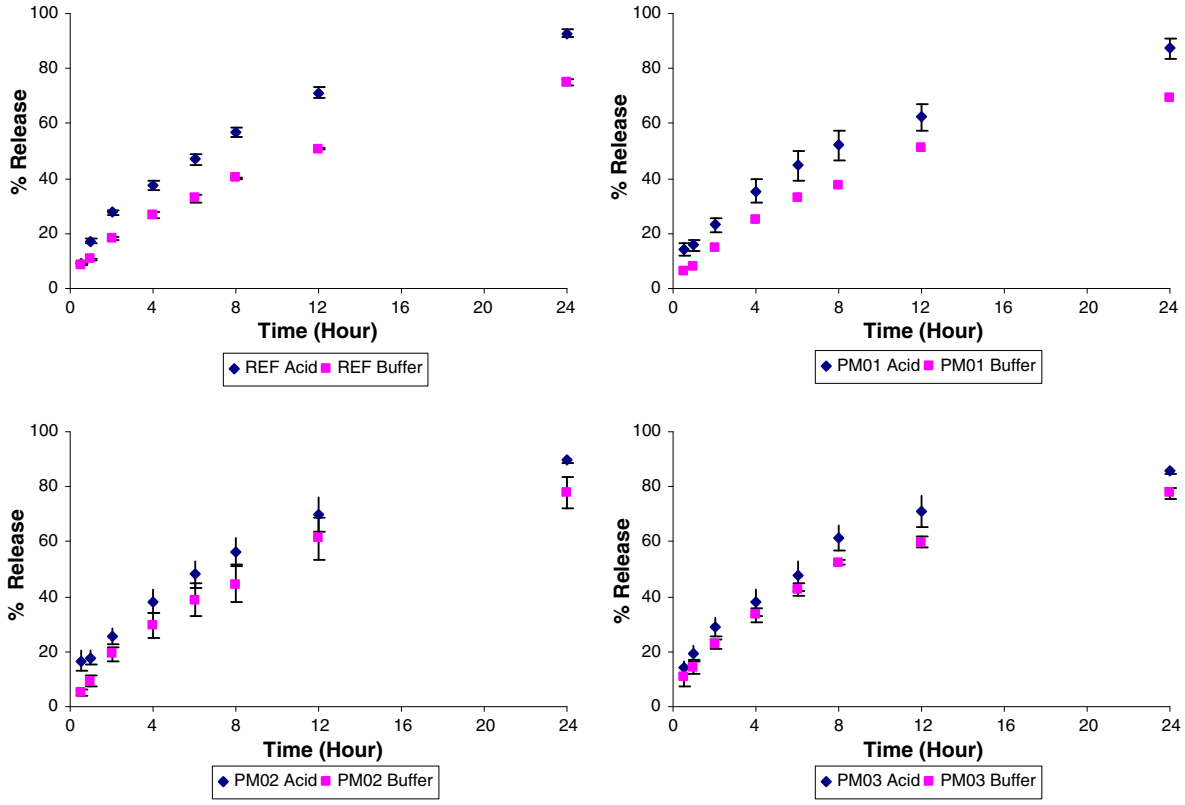


Fig. 4. Effect of pH on drug release from PM formulas.

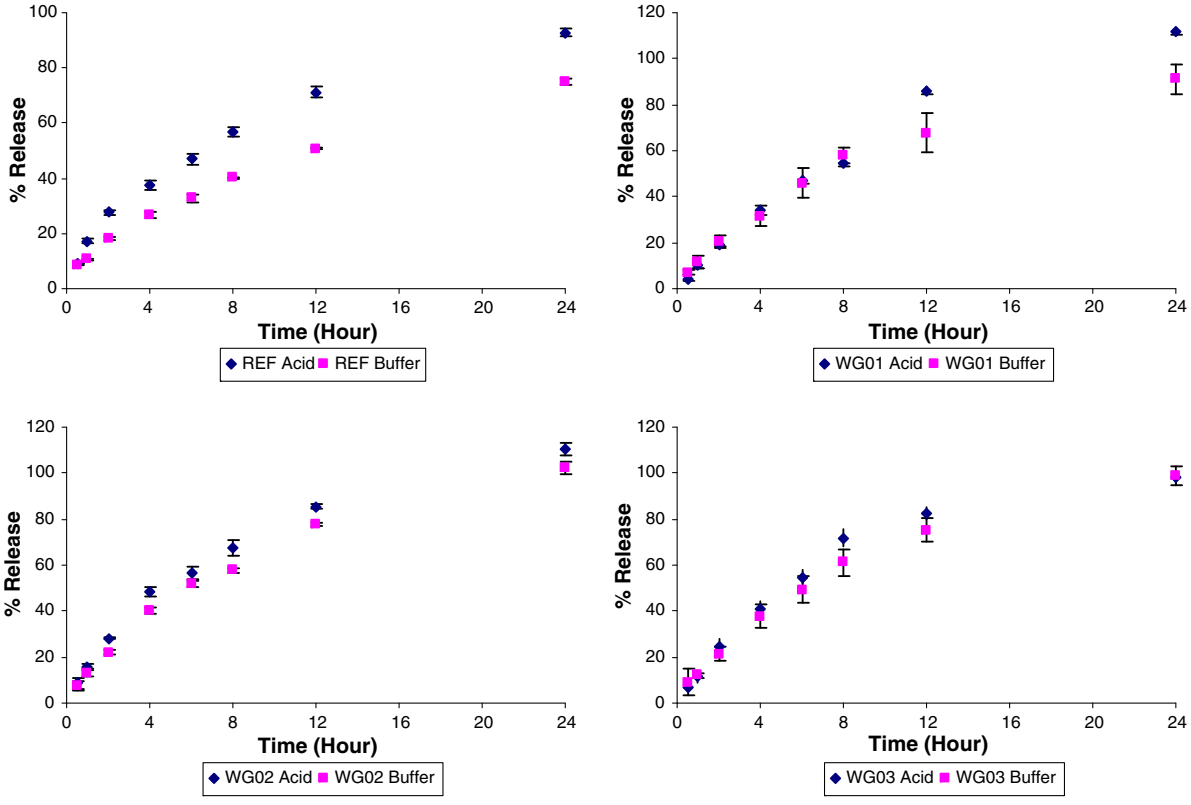


Fig. 5. Effect of pH on drug release from WG formulas.

Table 2
Kinetic analysis of the effect of CS content and mode of incorporation on drug release in different media using the first 60% of the release curves

Dissolution medium	Formula	K (hour^{-n}) (95% CI)	n (95% CI)	R^2	MDT (hour)
Acid	REF	0.159 (0.139–0.183)	0.625 (0.521–0.729)	0.9858	7.291
	PM01	0.178 (0.154–0.205)	0.498(0.392–0.605)	0.9767	10.639
	PM02	0.202(0.172–0.237)	0.468 (0.346–0.591)	0.9656	9.723
	PM03	0.199 (0.184–0.216)	0.505 (0.444–0.567)	0.9923	8.207
	WG01	0.089 (0.072–0.109)	0.936 (0.781–1.090)	0.9859	6.409
	WG02	0.156 (0.136–0.179)	0.772 (0.645–0.899)	0.9919	4.834
	WG03	0.123 (0.108–0.140)	0.855 (0.737–0.974)	0.9943	5.346
Buffer	REF	0.119 (0.109–0.131)	0.574 (0.511–0.637)	0.9909	14.875
	PM01	0.091 (0.832–0.989)	0.698 (0.642–0.754)	0.9952	12.743
	PM02	0.095 (0.083–0.109)	0.773 (0.685–0.861)	0.9903	9.161
	PM03	0.153 (0.143–0.164)	0.565 (0.519–0.609)	0.9952	10.013
	WG01	0.118 (0.112–126)	0.752 (0.706–797)	0.9981	7.360
	WG02	0.129 (0.118–0.142)	0.759 (0.688–0.829)	0.9955	6.409
	WG03	0.136 (0.119–0.155)	0.715 (0.617–813)	0.9903	6.790
Water	REF	0.041 (0.025–0.066)	1.246 (0.868–0.1.623)	0.9545	7.202
	PM01	0.071 (0.062–0.081)	0.91 (0.811–1.010)	0.9938	8.717
	PM02	0.069 (0.059–0.087)	1.005 (0.805–1.206)	0.9884	7.168
	PM03	0.078 (0.064–0.097)	0.949 (0.772–1.127)	0.9897	7.160
	WG01	0.109(0.103–0.118)	0.744 (0.692–0.795)	0.9975	8.391
	WG02	0.115 (0.084–0.157)	0.82 (0.584–1.056)	0.9588	6.298
	WG03	0.111(0.0964–0.129)	0.897(0.767–1.028)	0.9938	5.483
NaCl	REF	0.107 (0.096–0.119)	0.704 (0.619–0.787)	0.9927	9.881
	PM01	0.178 (0.166–0.190)	0.614 (0.563–0.666)	0.9964	6.325
	PM02	0.189 (0.177–0.202)	0.624 (0.564–0.684)	0.9973	5.548
	PM03	0.095(0.083–0.109)	1.019 (0.895–1.144)	0.9956	5.085
	WG01	0.176 (0.158–0.195)	0.649(0.557–0.743)	0.9939	5.722
	WG02	0.1571 (0.152–0.163)	0.751(0.719–0.782)	0.9995	5.043
	WG03	0.141(0.134–0.148)	0.837(0.792–0.883)	0.9991	4.732

evident from the f_2 values the formulas where CS was incorporated by wet granulation with BUSP where it reached 50.02, 58.45 and 63.41 for the formulas WG01, WG02 and WG03, respectively.

This can be explained by the more effective interaction between CS and BUSP when incorporated in a more intimate form in the formulation and is supported by the previously discussed DSC results.

The kinetic analysis of the dissolution data is shown in Table 2. The results show a 50.783% change in the MDT values of the reference formula without CS when between dissolution profiles in 0.1 N HCl and phosphate buffer. The change in MDT decreases as a function of CS content. However, the order of the MDT difference was not identical to that found using the f_2 statistic with values of 16.510%, −6.136% and 18.039% for formulas PM01, PM02 and PM03, respectively, and values of 12.917%, 24.572% and 21.262% for the formulas WG01, WG02 and WG03, respectively.

This apparent discrepancy is probably due to the differences in the sets of data used to calculate the two parameters. While the f_2 statistic used the whole dissolution profile, the Peppas–Korsmeyer

Table 3
Kinetic analysis of the effect of CS content and mode of incorporation on drug release in different media using complete release curves

Dissolution medium	Formula	K (hour^{-n})(95% CI)	n (95% CI)	R^2	MDT (hour)
Acid	REF	0.163 (0.143–0.185)	0.584 (0.514–0.655)	0.9858	8.235
	PM01	0.178 (0.161–0.196)	0.501 (0.447–0.555)	0.9885	10.462
	PM02	0.202 (0.179–0.227)	0.476 (0.412–0.542)	0.9818	9.287
	PM03	0.202 (0.185–0.219)	0.485 (0.438–0.532)	0.9907	8.837
	WG01	0.0918 (0.073–0.115)	0.864 (0.741–0.986)	0.9802	7.353
	WG02	0.162 (0.134–0.193)	0.67 (0.570–0.763)	0.9794	6.070
	WG03	0.13 (0.102–0.166)	0.734 (0.601–0.868)	0.9678	6.820
	REF	0.119 (0.110–0.129)	0.576 (0.531–0.621)	0.9939	14.717
	PM01	0.092 (0.083–0.102)	0.67 (0.613–0.728)	0.9927	14.124
	PM02	0.098 (0.081–0.118)	0.718 (0.617–0.821)	0.9803	10.619
Buffer	PM03	0.155 (0.142–0.170)	0.538 (0.488–0.588)	0.9915	11.189
	WG01	0.122 (0.107–0.139)	0.687 (0.613–0.761)	0.9886	8.704
	WG02	0.134 (0.116–0.154)	0.696 (0.617–0.775)	0.9872	7.368
	WG03	0.139(0.121–0.161)	0.664 (0.587–0.742)	0.9865	7.792
	REF	0.044 (0.027–0.074)	1.049 (0.770–1.327)	0.9339	10.056
	PM01	0.074 (0.059–0.093)	0.804 (0.680–0.927)	0.9769	11.362
	PM02	0.074 (0.055–0.099)	0.827 (0.665–0.989)	0.9632	10.546
Water	PM03	0.083 (0.063–0.108)	0.789 (0.642–0.935)	0.9666	10.338
	WG01	0.113 (0.099–0.129)	0.685 (0.613–0.758)	0.9889	9.805
	WG02	0.121 (0.089–0.166)	0.697 (0.525–0.868)	0.9425	8.502
	WG03	0.117 (0.093–0.148)	0.76 (0.633–0.888)	0.9724	7.267
NaCl	REF	0.108 (0.098–0.118)	0.701 (0.649–0.752)	0.9945	9.860
	PM01	0.184 (0.156–0.216)	0.556 (0.466–0.646)	0.9745	7.505
	PM02	0.196 (0.165–0.232)	0.573 (0.480–0.607)	0.9741	6.260
	PM03	0.103 (0.074–0.142)	0.847 (0.669–1.024)	0.9577	19.241
	WG01	0.181 (0.152–0.214)	0.613 (0.519–0.709)	0.9775	6.177
	WG02	0.164 (0.134–0.201)	0.675 (0.563–0.788)	0.9729	5.868
	WG03	0.149 (0.116–0.192)	0.731 (0.593–0.869)	0.9654	5.711

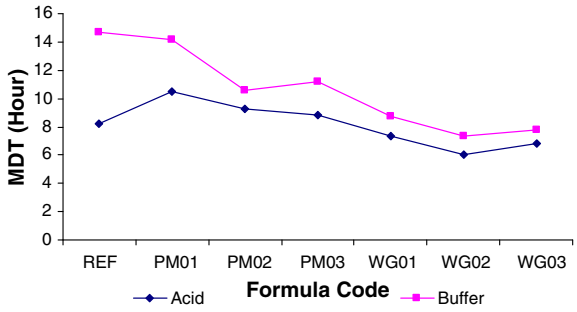


Fig. 6. Effect of CS content and mode of incorporation on MDT (calculated using entire release profile).

parameters and the derived MDT are derived from partial dissolution data as their use is confined to the first 60% of the release curve [3].

However, some authors suggested that the Peppas–Korsmeyer equation can be used to describe the entire drug release curve from HPMC-based matrix tablets [36]. Using this approach to calculate the Peppas–Korsmeyer parameters and MDT produced results of MDT that were more consistent with those of the f_2 statistic and the DSC results as shown in Table 3 and Fig. 6.

3.5.2. Effect of ionic strength on the drug release

The effect of the ionic strength of the dissolution medium on drug release from HPMC matrices has long been the topic of research with some findings suggesting that increased ionic strength results in accelerated dissolution [37], while others suggesting the opposite [38].

The objective of our dissolution experiments in deionized water and 5% NaCl solutions (ionic strength 0.86) was to get an insight into the ionic nature of interaction between CS and BUSP based on the hypothesis that a higher ionic strength dissolution medium will promote an ion exchange process between the CS–BUSP complex and the dissolution medium thus accelerating the release of BUSP from the HPMC matrix.

The drug release results in deionized water and 5% NaCl are shown in Figs. 7 and 8. It was evident that the drug release increased in the 5% NaCl solution in comparison to deionized water for all formulas. In order to evaluate the effect of the ionic strength quantitatively, the release profiles were compared using the f_2 statistic and MDT calculated from the Korsmeyer–Peppas parameters for the "entire" dissolution data rather than the first 60% portion.

The f_2 value obtained by setting the release profile in water as a reference profile and the release profile in 5% NaCl solution as a test profile was 40.66 for the REF formulation. The f_2 values for the formulas PM01, PM02 and PM03 were 44.81, 33.53 and 31.91, respectively, reflecting a gradual increase in the difference between the test and reference profiles for each formula in the two media as the content of CS increases and the contribution of the ionic interaction increases in the overall drug release.

On the other hand, the f_2 values for the formulas WG01, WG02 and WG03 were 38.58, 36.18 and 57.01, respectively. The unexpected increase in the value of the f_2 statistic of WG03 is most probably due to the fact that the release profile of WG03 in 5% NaCl solution reached a plateau after 10 h (105.53 ± 3.57 at 10 h and 105.95 ± 3.75 at 12 h) allowing the release profile of WG03 in water to catch up and reduce the dissimilarity based on the f_2 statistic which is a cumulative value.

In order to test the aforementioned hypothesis, the f_2 statistic was calculated using the data points up to 10 h for the REF and WG formulas and results were 51.64, 25.28, 21.11 and 28.96 for the formulas REF, WG01, WG02 and WG03, respectively. These results confirm

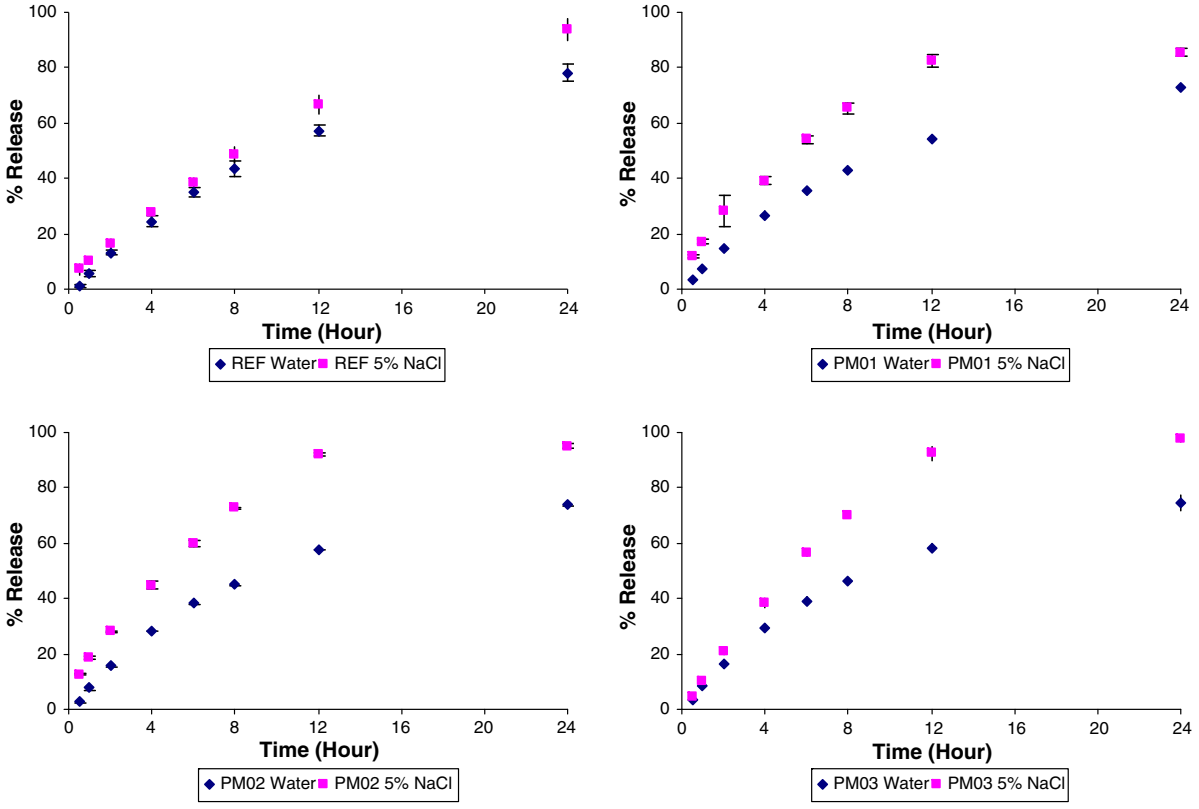


Fig. 7. Effect of ionic strength on drug release from PM formulas.

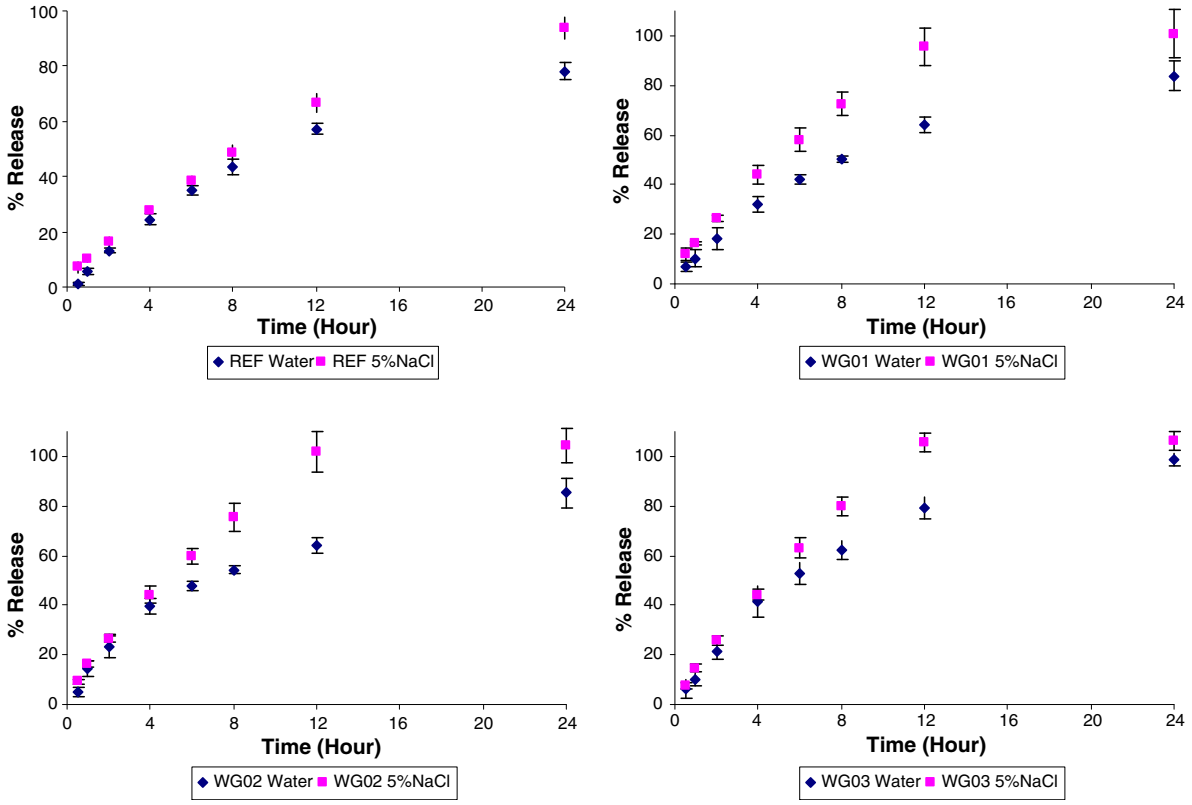


Fig. 8. Effect of ionic strength on drug release from WG formulas.

Table 4
MDT and % difference MDT analysis of the effect of CS content and mode of incorporation on drug release in water and 5% NaCl solution (calculated using complete release curves)

Formula	MDT (hour)		MDT % change
	Water	5% NaCl	
REF	10.056	9.860	−1.949
PM01	11.362	7.505	−33.948
PM02	10.546	6.260	−40.639
PM03	10.338	6.713	−35.071
WG01	9.805	6.177	−37.001
WG02	8.502	5.868	−30.978
WG03	7.267	5.711	−21.419

the above hypothesis of the effect of the release plateau on the f_2 statistic and that the effect of the ionic strength of the medium is most evident in formulations containing CS, where an ionic interaction–ion exchange mechanism is involved in drug release.

A similar conclusion may be made when using the MDT data presented in Table 4 to evaluate the effect of the ionic content of the dissolution media on the BUSP release. The % difference in MDT was least in the REF formulation with a value of (−1.949) and ranged between (−21.419) and (−40.639) for the different PM and WG type formulations indicating a much greater sensitivity of the CS containing formulations towards the ionic content of the dissolution media.

4. Conclusions

The anionic CS was proved effective in modulating the release of BUSP from HPMC-based matrices. This is most likely due to complexation with the cationic drug, the extent of which was found to be dependent on the method of preparation.

The inclusion of CS in HPMC matrices decreased the difference in release rates of BUSP in 0.1 N HCl and USP phosphate buffer, pH 6.8, and its efficacy in modulating BUSP release was dependent on both the level and mode of incorporation of CS. The nature of the ionic interaction and release mechanism has been substantiated by observing an accelerated dissolution in media with higher ionic strengths.

CS is a novel material with potential for formulating solid dosage forms of cationic drugs intended for pH-independent target release.

Acknowledgements

The authors acknowledge the financial support received from the Deanship of Scientific Research at the University of Jordan under the research Grant 99/2004-2005 and the Jordanian Pharmaceutical Manufacturing Co (JPM) for the generous donation of BUSP.

The authors also acknowledge the technical help of Ms. Hadil Hudaib, Ms. Lina Sakran and Mr. Tareq Najjar. The authors also thank Prof. Adnan Dakkuri, Ferris State University, for his help in reviewing the manuscript and the many useful suggestions.

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