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RESEARCH ARTICLE

Evaluation of hydrophilic matrix tablets based on Carbopol® 971P and low-viscosity sodium alginate for pH-independent controlled drug release

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Abstract

Background: The aim of this study was to evaluate matrix tablets containing different ratios of Carbopol® 971P (CP) to low-viscosity sodium alginate (SA) and assess their suitability for pH-independent controlled drug release.

Methods: Two processing methods (physical mixing, PM and spray-drying, SD) were applied before compaction and the release from corresponding matrices was compared. The release from CP-SA PM matrices was also investigated using three model drugs (paracetamol, salicylic acid, and verapamil HCl) and two dissolution media (0.1 N HCl or phosphate buffer, pH = 6.8), and the release rate, mechanism, and pH-dependence were characterized by fitting of Higuchi and Peppas models, and evaluation of similarity factor. Furthermore, swelling behavior of CP-SA matrix tablets was studied for evaluating its impact on drug release.

Results: The processing method (SD or PM) markedly affected the drug release from CP-SA matrices. ANOVA tests showed significant effects of the CP:SA ratio and drug type on the release rate (expressed by the constant, K_H, from Higuchi model) and of the dissolution medium on the release mechanism (expressed by the exponent, n, from Peppas model). Similarity factor (f_2) indicated that the CP:SA ratios ≥ 25:75 and ≥ 50:50 were suitable for pH-independent release of paracetamol and salicylic acid, respectively, although for verapamil HCl, the matrix with low CP:SA ratio (0:100) showed remarkably reduced pH-dependence of release. Swelling parameters (water uptake and mass loss) were significantly changed with experimental variables (CP:SA ratio, medium, and time) and were in good correlation with drug release.

Conclusion: Matrix tablets based on CP and SA form a potentially useful versatile system for pH-independent controlled drug release.

Keywords: *pH-independent release*, *similarity factor*, *spray-drying*, *swelling*, *erosion*

Introduction

Water-swellable polymer (hydrophilic colloid) matrices represent a simple and flexible approach to controlled drug delivery[1]. Combination of polymers in such matrices has been frequently applied to enable controlling drug release by adjusting the ratio of the combined polymers in the matrix former. Recently, there is an increased interest in using combinations containing ionizable polymers of pH-dependent swelling and erosion in CR matrix formulations. Such combinations are designed to minimize pH-dependent release, which is a common problem with peroral CR dosage forms that frequently causes *in vivo* variability and bioavailability problems and usually occurs with drugs exhibiting pH-dependent solubility and dissolution rate in the pH range of the gastrointestinal tract[2]. Polymer combinations of xanthan gum with chitosan[3] and of HPMC with carrageenan[4], sodium alginate (SA)[5], and chitosan succinate[6] have been employed for this purpose.

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Among the ionizable polymers, acrylic acid polymers (Carbomers, Carbopols®) and SA are increasingly used as hydrophilic matrix formers in controlled release systems[7,8].

Carbopols® are synthetic high-molecular-weight polymers of acrylic acid cross-linked with either allylsucrose or allylethers of pentaerythritol. Due to presence of carboxylic acid groups in the polymer chain, the pH of their aqueous solution (1%) ranges from 2.5 to 3.0[7]. An increased interest has been shown by researchers in the application of Carbopols® as matrix formers in oral-controlled release dosage forms[9–11] and gastric retentive systems[12–15]. Among the grades used in oral dosage forms, Carbopol® 971P (CP) NF is lightly cross-linked and in matrix tablets, it swells more rapidly in neutral than in acidic media forming thicker and more viscous homogeneous gel layer that leads to higher retardation of release as demonstrated by several researchers[9,10,13].

SA is the sodium salt of alginic acid, a high-molecular-weight natural polysaccharide derived from seaweeds and composed of varying amounts of (1–4)-linked β-D-mannuronic acid and α-L-guluronic acid residues. It has a known pH-dependent release retarding capability in a matter, which was found to be noticeably affected by viscosity grade. More specifically, Efentakis and Buckton[16] reported that the release of theophylline from SA matrices was very fast for the low-viscosity (LV) grade in water and for the high-viscosity (HV) grade in 0.1 N HCl, whereas they observed slow release for LV in the acidic medium with very slow release for the HV in water. Similar confirmatory results were reported later by Liew et al.[17] who found that the release of chlorpheniramine maleate from SA matrices was slower for LV than for HV in acidic medium (pH = 1.2). However, when the pH of the medium was increased to 6.8, the release from matrices containing LV increased remarkably and became faster than from those containing HV.

Since it has been demonstrated by previous studies that LV SA, as a matrix former, results in more rapid release in neutral than in acidic media, although CP results in an opposite effect (i.e. slower release in neutral media), the combination of both polymers seems interesting as a universal matrix former to achieve pH-independent controlled release of drugs with different properties (i.e. neutral, acidic, and basic) by adjusting the ratio of the two polymers in the matrix former. A major advantage of this combination is that both polymers are anionic, a matter that excludes the formation of inter-polyelectrolyte complex, which might complicate the release from matrices and diminish the preferred pH-dependent swelling of polymers. However, up to our knowledge, such combination has not been evaluated previously in terms of its ability to achieve pH-independent release, and only one research paper evaluated the ratio of CP and SA in the matrix former and water:ethanol ratio in the granulation liquid on rate and mechanism of amoxicillin release in 0.1 N HCl from potentially floating tablets[12].

Spray-drying (SD) has been widely used in the pharmaceutical field for preparation of sustained release microparticles that usually have good flow and compression properties and therefore are appropriate for further compression into matrix tablets[18]. Matrices prepared using spray-dried mixtures may show different release profiles from equivalents prepared using physical mixtures as reported for matrix tablets based on Carbopol® 974P and Amioca starch[19].

In this work, polymer mixtures comprised of CP and LV SA were evaluated as hydrophilic matrix formers for pH-independent controlled drug release. Physical mixing (PM) and SD were investigated as two methods for processing of drug and polymers prior to compression into matrix tablets. Paracetamol, salicylic acid, and verapamil HCl were selected as model drugs of neutral, acidic, and basic properties, respectively.

Materials

The polymers used were CP (from Lubrizol, Wickliffe, OH, USA), kindly donated by JPM, Amman, Jordan, and SA, from BDH, Poole, Dorset, UK. The viscosity of 2% w/v polymer solution in distilled water at 25°C was determined using the Cup and bob method on Physica MCR 301 rheometer (Anton Paar, Austria) at shear rate 100 sec^{-1} and was found to be 0.606 and 0.121 Pa×sec for CP and SA, respectively. Model drugs used were: (1) paracetamol, kindly donated by Midpharma, Amman, Jordan, (2) salicylic acid from Gainland Chemical Company (GCC), UK, and (3) verapamil HCl from Medex, Naseby, Northants, UK. All polymers and drugs used were in powder form. All other reagents and materials were of analytical grade and were used as supplied.

Methods

Preparation of spray-dried paracetamol microparticles

Microparticles were prepared by cospray-drying paracetamol, as a model drug, with CP and SA at three different CP:SA ratios (100:0, 50:50, and 0:100) in order to evaluate the feasibility of obtaining spray-dried microparticles and to compare matrix tablets prepared by tableting the SD microparticles, regarding release behavior, with those prepared by tableting physical mixtures. The solutions for SD were of 1:1 paracetamol:polymer(s) ratio and fixed total concentration (1%) in all runs and were prepared as follows. Polymer solutions of different CP:SA (CP:SA) ratios (0:100, 50:50, and 100:0) but fixed total concentration were prepared, each by dissolving 5 g of polymer(s) in 1-L glass beaker containing 500 mL distilled water under magnetic stirring, which was continued for 24 h to ensure complete dissolution. Five grams of paracetamol was dissolved separately in 400 mL distilled water, and then the paracetamol solution was mixed with the polymer solution and the volume completed to 1000 mL. The solutions were spray-dried using Pulvis GA 32 minispray (Yamato Scientific, Japan) equipped with a standard 406-μm spray nozzle. The operation conditions were inlet air temperature 125–127°C, outlet

air temperature 65–75°C, spray pressure 1 kg/cm^2, and spray feed rate 4 mL/min. The microparticles accumulated in the product vessel were collected, weighed, and kept in screw-capped plastic containers until required for examination.

Drug content determination

Accurately weighed samples (about 10 mg) of each spray-dried batch were dissolved in 100 mL distilled water with the aid of an orbital shaker (SO1; Stuart Scientific, Staffordshire, UK). The drug (i.e. paracetamol) content was determined, after appropriate dilution, using UV spectrophotometer (Spectronic 601; Milton Roy, Ivyland, PA, USA) at wavelength corresponding to maximum absorbance (λ_{max} = 244 nm). The encapsulation efficiency was expressed as percentage of the actual amount of drug to the theoretical (initially added) amount. The procedure was carried out in triplicate and the average and standard deviation was determined.

Scanning electron microscopy

Size and morphology of the collected spray-dried microparticles was evaluated by scanning electron microscopy (SEM; Zeiss Ultra Plus, Carl Zeiss NTS GmbH, Germany). Samples were mounted on aluminum stubs with double-sided sticky discs of conductive carbon and then coated with ~15 nm of gold in a sputter coater (Emitech K550X, Ashford, Kent, UK).

Preparation of matrix tablets

For comparison, paracetamol matrix tablets were prepared from spray-dried microparticles and equivalent physical mixtures (i.e. of similar composition). The 480 mg of spray-dried particles, containing theoretically 240 mg of paracetamol, was directly compacted in a 13-mm diameter round flat-faced punch and die set using manual hydraulic press (Shimadzu, Kyoto, Japan) at pressure 20 MPa for 30 sec. Equivalent matrix tablets from physical mixtures were prepared by mixing equal amounts of paracetamol and matrix former (CP, SA, or a 50:50 binary mixture of them) using a spatula for 15 min, and then 480 mg of the powder mixture was compressed as described for the spray-dried microparticles.

In addition, for investigation of release behavior of drugs with different physicochemical properties from CP-SA matrices in acid and buffer media, matrix tablets from physical mixtures were prepared according to the method described above using paracetamol, salicylic acid, and verapamil HCl as model drugs of neutral, acidic, and basic properties, respectively, and five different CP:SA ratios (0:100, 25:75, 50:50, 75:25, and 100:0). In all physical mixtures, components size fraction <180 μm obtained by sieving was used.

In vitro drug release

Release study was performed in a USP Apparatus II paddle system (Pharma Test PTW 2, Hainburg, Germany) at 100 rpm using 900 mL of dissolution medium at a temperature of 37 ± 0.5°C. The paddle instead of the basket system was used in order to avoid possible interference with the swelling of the matrix tablets and the release process, since the tablets are relatively large and contain highly swellable polymers[20]. Distilled water (pH = 6.5) was used as dissolution medium for comparison between paracetamol SD and PM matrices. Phosphate buffer (pH = 6.8) and 0.1 N HCl (pH = 1.2) were used as dissolution media to study the effect of pH on release of different model drugs (neutral, acidic, and basic) from PM matrices containing different CP:SA ratios, in order to elucidate the suitable composition for pH-independent controlled release for each model drug.

At predetermined time intervals, samples were taken and filtered through 0.45-μm cellulose acetate syringe filters and the concentration of drug dissolved was determined by UV spectroscopy at wavelength corresponding to maximum absorbance (λ_{max} = 244, 297, and 278 nm for paracetamol, salicylic acid, and verapamil HCl, respectively). All tests were performed in triplicates.

Release data modeling

In order to characterize the release mechanism, the power law model of Peppas was fitted to the first 60% release data[21]:

$$M_t/M_\infty = K_p t^n \quad (1)$$

where M_t/M_∞ represents the fractional release of drug, K_p is the release rate constant, and n is the release exponent indicative of the drug release mechanism. In the case of cylindrical tablet, a value of $n \leq 0.45$ indicates Fickian diffusion, $0.45 \leq n \leq 0.89$ indicates non-Fickian (anomalous) diffusion, $n = 0.89$ indicates case-II transport (erosion control and zero-order kinetics), and $n \geq 0.89$ indicates Super Case II transport[22].

In order to compare the release profiles of formulas with possible difference in release mechanisms (n values), the square root model of Higuchi was fitted to the release data:

$$M_t = K_H t^{0.5} \quad (2)$$

where M_t is the amount of drug released at time t and K_H is the Higuchi release rate constant.

Matrix swelling studies

Swelling behavior was evaluated for paracetamol PM matrix tablets of different CP:SA ratios in the matrix former using 0.1 N HCl and phosphate buffer (pH = 6.8) under conditions identical to those described above for release testing. At three time intervals (2, 4, and 6 h), tablets were gently withdrawn from the dissolution media using a spoon spatula and excess liquid was blotted from around the swelled tablets carefully to avoid touching and deforming them. The matrix tablets were then weighed and dried at 70°C to a constant weight. Swelling parameters were determined according to the following equations:

$$\text{Water uptake}\,(\%) = (W_W - W_d)\times 100/W_d \quad (3)$$

$$\text{Mass loss}\,(\%) = (W_i - W_d)\times 100/W_i \quad (4)$$

where W_i is the initial tablet weight, W_w is the weight of wet tablet after immersion into the dissolution medium, and W_d is the weight of dried tablet after immersion into the dissolution medium and drying to constant weight.

Morphological examination of the swollen tablets was also carried out on each tablet formulation after immersion in 0.1 N HCl or phosphate buffer (pH = 6.8) for 1 h. The tablets were taken out from the medium and were imaged using a digital camera (EasyShare Z1285, KODAK, Rochester, NY, USA).

Statistical analysis

Analysis of variance (ANOVA) tests at the significance level of 0.05 were applied to evaluate the statistical significance of the main effects and two-way interactions of: (1) CP:SA ratio, dissolution medium, and drug type on the parameters used to express the rate and mechanism of release (Higuchi rate constant, K_H, and exponent n of the power law model, respectively) and (2) CP:SA ratio, dissolution medium, and time on swelling parameters (water uptake and mass loss). For statistical analysis, the program SPSS 14.0 (Chicago, IL) was used.

Results and discussion

Production yield and encapsulation efficiency

The results of production yield and encapsulation efficiency for microparticles prepared by SD paracetamol with CP and SA at three different CP:SA ratios (0:100, 50:50, and 100:0) are given in Table 1. It can be seen that the production yield, which is expressed as the mass percentage of the harvested microparticles to the initial mass of drug and polymer(s), was low (<28%) and the encapsulation efficiency was high (around 100%). The low yield values, which are quite frequent in SD methods[23], are probably due to high adhesion of the sprayed droplets to the internal surfaces of drying chamber and cyclone before they dry and reach the product vessel.

SEM micrograph

SEMs for the spray-dried microparticles are presented in Figure 1. They show that the size of individual microparticles was generally <10 μm. They also show that for the three spray-dried products prepared using different CP:SA ratios, microparticles were nearly spherical in shape with rough surface and a high degree of aggregation. The roughness of surface is probably due to crystallization of paracetamol and is most clearly seen in the case of paracetamol-CP spray-dried microparticles (Figure 1A), and this difference in roughness may be

Table 1. Production yield and encapsulation efficiency for spray-dried paracetamol microparticles obtained using different Carbopol® 971P:sodium alginate (CP:SA) ratios.

CP:SA ratio	Production yield (%)	Encapsulation efficiency (%) mean ± SD
0:100	20.8	99.3 ± 1.4
50:50	27.7	98.8 ± 0.9
100:0	24.6	101.6 ± 0.8

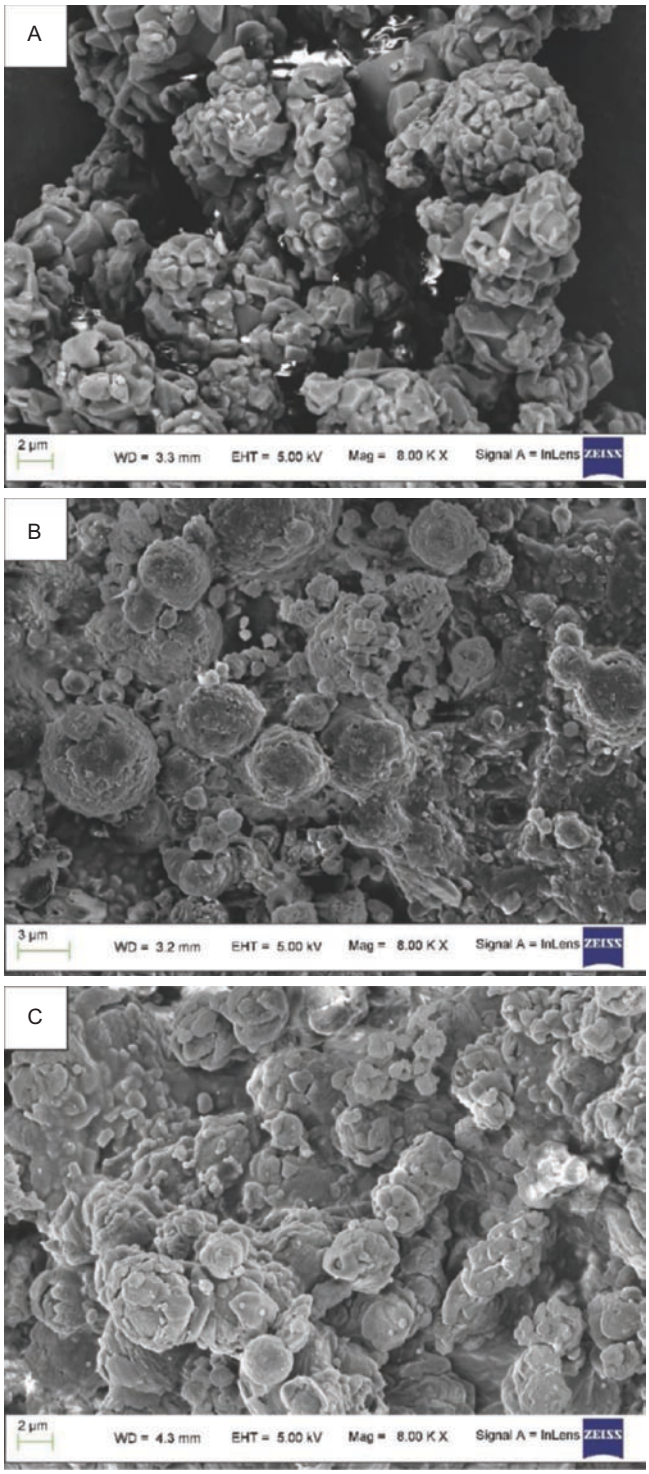

Figure 1. Scanning electron micrographs for microparticles prepared by cospray-drying paracetamol with Carbopol® 971P (CP) and sodium alginate (SA) at CP:SA ratios of 100:0 (A), 50:50 (B), and 0:100 (C).

due to a difference in paracetamol crystal growth rate between the different polymeric solutions

In vitro drug release behavior of CP-SA matrix tablets

The release profiles of paracetamol, in distilled water, from matrix tablets prepared by PM and SD are shown in Figure 2. The two processing methods (PM and SD) usually lead to different degrees of mixing where PM results in distribution of drug and polymer particles and SD of solutions usually results in blending and distribution at molecular level and may affect the solid state of the processed materials. From Figure 2, it can be seen that the release rate increases with increasing SA ratio, for both PM and SD matrix tablets. This is consistent with previously reported results by Tapia-Albarran and Villafuerte-Robles[12] and indicates lower release sustaining capability, probably due to faster and easier swelling and erosion, of SA (which is a LV grade) than CP. Interestingly, the release profiles of SD matrices were different from those of the corresponding PM matrices in a manner depending on CP:SA level. More specifically, the drug release was slower from SD matrices than from PM matrices in the cases of 0:100 and 100:0 CP:SA ratios (i.e. either SA or CP as a matrix former), although at 50:50 CP:SA ratio slower release from PM matrices than from SD matrices was observed (Figure 2). Differential scanning calorimetry (DSC) testing of spray-dried samples and equivalent physical mixtures (data not shown) did not help to explain the drug release behavior and no interaction between the two polymers has been detected. The slower release from SD matrix tablets in the cases where either SA or CP were used might be explained by more uniform polymer distribution and swelling[24], whereas the faster release from SD matrices in the case of 50:50 CP:SA ratio might be due to faster swelling and erosion of CP by cospray-drying with the LV SA.

The release profiles in two dissolution media (0.1 N HCl, pH = 1.2 or phosphate buffer, pH = 6.8) for PM matrix tablets with different CP:SA ratios and paracetamol, salicylic acid, or verapamil HCl, as model drugs, are shown in Figures 3–5, respectively. The results of fitting the release data to power law and square root models are presented in Table 2. The results of ANOVA showing the significance of CP:SA ratio, dissolution medium, drug type, and two-way interactions on Higuchi release rate constant (K_H) and release exponent (n) from power law fitting are given in Table 3.

From Table 2, it can be seen that the release data were better-fitted by the power law model of Peppas than by the square root model of Higuchi as indicated by higher correlation coefficient values. Furthermore, it can be seen that the release exponent (n) values range between 0.547 and 1.259 indicating that the release mechanism ranges

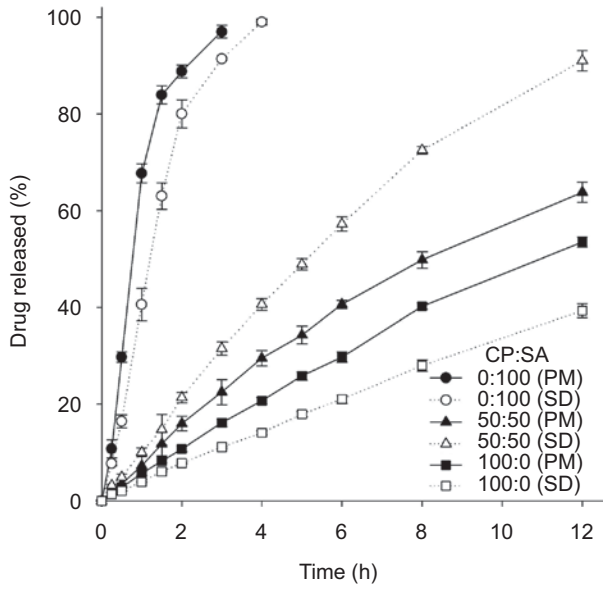

Figure 2. Release profiles of paracetamol in distilled water (pH = 6.5) from matrix tablets containing Carbopol® 971P (CP) and sodium alginate (SA) at different ratios prepared by spray-drying (SD) and physical mixing (PM). Error bars represent standard deviation.

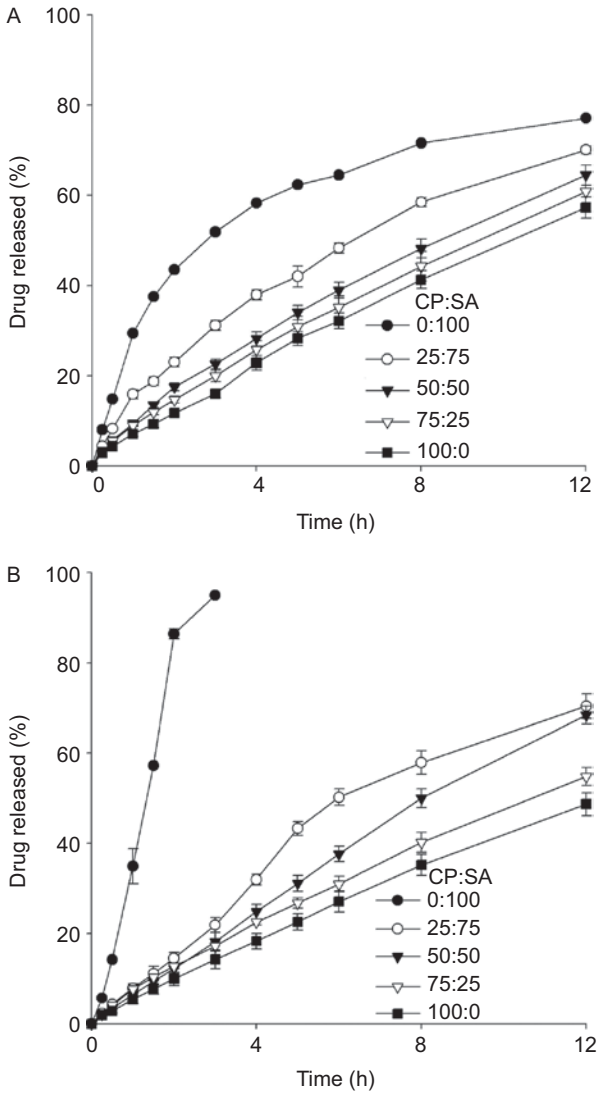

Figure 3. Release profiles of paracetamol in 0.1 N HCl (A) and phosphate buffer, pH = 6.8 (B) from PM matrix tablets containing Carbopol® 971P (CP) and sodium alginate (SA) at different ratios. Error bars represent standard deviation.

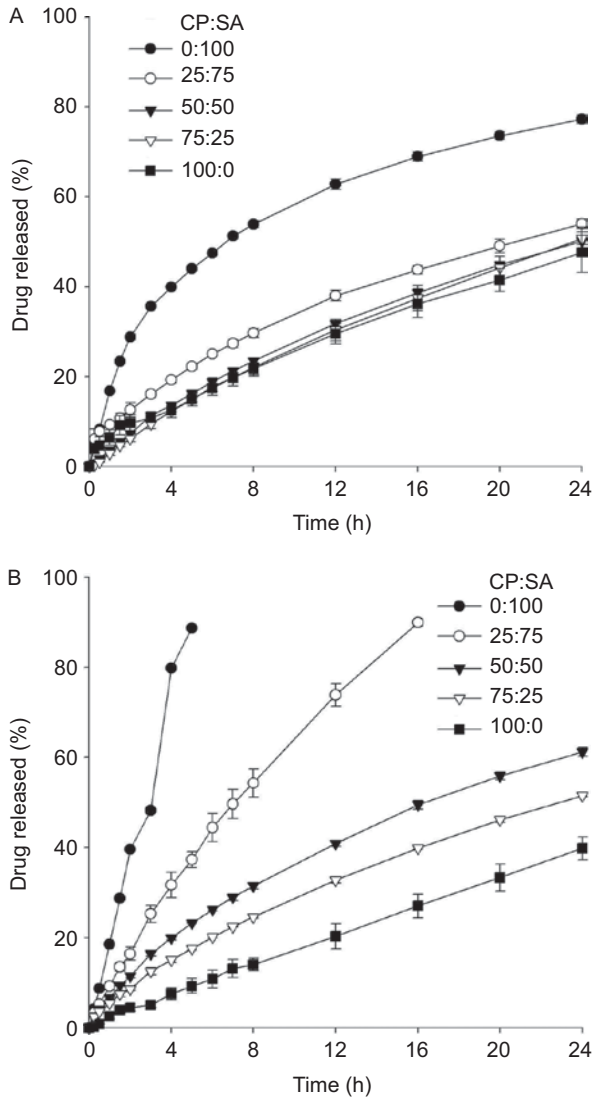

Figure 4. Release profiles of salicylic acid in 0.1 N HCl (A) and phosphate buffer, pH = 6.8 (B) from PM matrix tablets containing Carbopol® 971P (CP) and sodium alginate (SA) at different ratios. Error bars represent standard deviation.

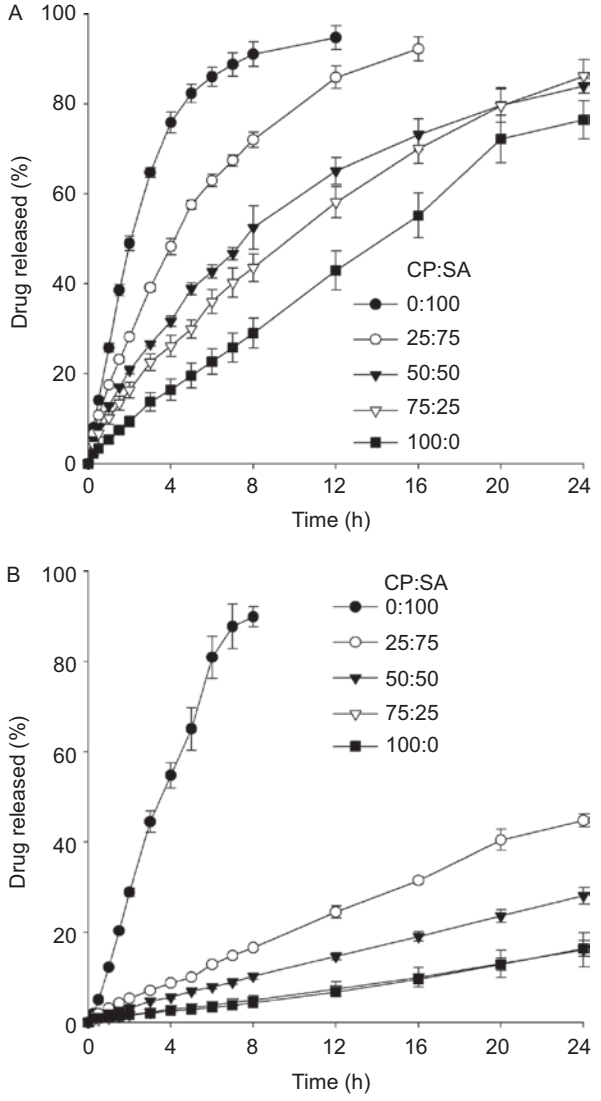

Figure 5. Release profiles of verapamil HCl in 0.1 N HCl (A) and phosphate buffer, pH = 6.8 (B) from PM matrix tablets containing Carbopol® 971P (CP) and sodium alginate (SA) at different ratios. Error bars represent standard deviation.

between anomalous diffusion and super case-II. Because of the variability in release mechanism, the Higuchi rate constant was used to describe the release rate to compare different release profiles.

The general trend of K_H values indicates that the release rate increased by increasing SA ratio for the three model drugs and both dissolution media, as seen also from Figures 3 to 5, which is again explained by the lower release sustaining capability of SA than that of CP in both media.

From Figures 3 to 5, it can also be seen that for a specific drug and dissolution medium, the release profiles of intermediate to high CP:SA ratio are close to each other in comparison with those of low CP:SA ratio (high SA content), which clearly exhibit faster release. Furthermore, it can be seen in Figures 4 and 5 that the profiles of high CP content are closer to each other in the medium where the drug solubility is reduced (i.e. 0.1 N HCl in the case of salicylic acid and buffer in the case of verapamil HCl). This indicates that the decrease in the release rate by increasing CP:SA ratio becomes less pronounced as CP content is increased and as drug solubility is reduced.

The effect of dissolution medium on release rate was different for the three model drugs. In the case of paracetamol matrices, K_H was higher in 0.1 N HCl than in buffer for all CP:SA ratios except the lowest (i.e. 0:100), whereas in the case of salicylic acid matrix tablets it was lower in 0.1 N HCl than in buffer for all CP:SA ratios except the highest (i.e. 100:0). In the case of verapamil HCl matrices, K_H was higher in 0.1 N HCl than in buffer for all CP:SA ratios and the K_H values were relatively close to those for paracetamol matrices in the case of 0.1 N HCl but much lower in the case of buffer indicating interaction between drug type and dissolution medium.

The faster paracetamol release in buffer than in 0.1 N HCl for matrix tablets of low CP:SA level and the slower

Table 2. Results of model fitting of release data to power law and square root models (release rate constants, K_p and K_H, exponent, n, and correlation coefficients, R) for CP-SA matrix tablets prepared from physical mixtures.

		0.1 N HCl					Phosphate buffer (pH = 6.8)				
		Power law model			Higuchi model		Power law model			Higuchi model	
Drug	CP:SA ratio	K_p (h^{-n})	n	R	K_H ($h^{-0.5}$)	R	K_p (h^{-n})	n	R	K_H ($h^{-0.5}$)	R
Paracetamol	0:100	0.272	0.584	0.986	26.00	0.972	0.345	1.259	1.000	49.06	0.920
	25:75	0.147	0.670	0.999	19.18	0.987	0.086	0.940	0.992	17.93	0.941
	50:50	0.092	0.766	1.000	15.80	0.965	0.071	0.829	0.999	15.26	0.924
	75:25	0.088	0.776	0.999	14.49	0.959	0.058	1.058	0.999	12.87	0.952
	100:0	0.069	0.853	0.999	13.19	0.942	0.053	0.906	1.000	11.06	0.937
Salicylic acid	0:100	0.180	0.547	0.987	17.59	0.984	0.194	0.874	0.985	32.42	0.921
	25:75	0.092	0.561	0.997	10.36	0.995	0.098	0.832	0.999	18.93	0.959
	50:50	0.049	0.740	0.997	8.93	0.965	0.078	0.665	0.998	11.59	0.983
	75:25	0.040	0.800	0.998	8.63	0.952	0.058	0.691	1.000	9.35	0.976
	100:0	0.054	0.683	0.994	8.49	0.976	0.021	0.927	0.999	6.19	0.927
Verapamil HCl	0:100	0.264	0.896	1.000	32.55	0.970	0.134	1.041	0.997	28.74	0.945
	25:75	0.173	0.744	1.000	24.04	0.988	0.026	0.907	0.999	7.24	0.934
	50:50	0.129	0.670	1.000	17.52	0.993	0.016	0.894	1.000	4.43	0.934
	75:25	0.101	0.704	1.000	16.26	0.981	0.006	1.000	0.998	2.37	0.912
	100:0	0.049	0.869	0.999	12.74	0.936	0.005	1.114	0.994	2.28	0.888

Table 3. ANOVA results for the effect of CP:SA ratio (X_1), dissolution medium (X_2), drug type (X_3), and two-way interactions on the release rate and mechanism (expressed by the Higuchi rate constant, K_H, from square root model and the exponent, n, from power law model, respectively).

	Higuchi rate constant (K_H)		Exponent of the power law model (n)	
Effect	F	P	F	P
X_1	43.537	<0.001	1.111	0.415
X_2	0.780	0.403	17.925	0.003
X_3	9.594	0.007	3.876	0.066
$X_1 \times X_2$	6.689	0.011	1.139	0.404
$X_1 \times X_3$	0.605	0.753	0.243	0.969
$X_2 \times X_3$	19.093	0.001	0.674	0.536

release in buffer for higher CP:SA levels is explained by the opposite changes in release retarding capability for the two polymers with changing pH of the dissolution medium. Specifically, by increasing pH, the release from CP matrices decreases due to increased swelling of the slowly erodible polymer, whereas the release from SA matrices increases due to rapid erosion. This is consistent with the findings of previous studies mentioned in the introduction[9,10,13,16,17]. For the matrix tablets containing salicylic acid and verapamil HCl, the pH-dependent solubility, that is, the higher solubility of the acidic drug in buffer and of the basic drug in acidic medium is another important factor that affects the release rate.

From Table 3 (ANOVA results), it can be seen that for the Higuchi rate constant (K_H), the main effects of CP:SA ratio and drug type were significant ($P \leq 0.001$ and = 0.007, respectively). The main effect of dissolution medium was not significant ($P = 0.403$) probably because of the absence of a simple clear trend due to significant interactions with CP:SA ratio ($P = 0.011$) and drug type ($P = 0.001$), which were noticed also in Table 2 as mentioned above. The two-way interaction between CP:SA ratio and drug type was nonsignificant ($P = 0.753$).

Regarding the release mechanism, it can be seen from Table 2 that the release exponent (n) values obtained by power law modeling were higher in phosphate buffer than in 0.1 N HCl except for two cases corresponding to salicylic acid matrices with CP:SA ratios of 50:50 and 75:25. It is reported for both CP and SA matrices that the release mechanism shifts from Fickian diffusion toward polymer swelling and relaxation by (1) increasing the pH of the dissolution medium, due to pH-dependent swelling of both polymers and (2) using less soluble drugs, which rely for their release on matrix erosion more than on diffusion of dissolved drug through the gel barrier[25,26]. Therefore, the higher n values in phosphate buffer (pH = 6.8) than in 0.1 N HCl (pH = 1.2) are in agreement with the reported similar shift in release mechanism for both polymers and in the case of verapamil HCl, this shift is also attributed to decrease of drug solubility in buffer. The absence of clear trend in the case of salicylic acid matrices is probably due to complicated combined effect of (1) changes in matrix swelling and erosion due to changing of pH inside the matrix by penetration of dissolution medium and dissolution of the acidic drug and (2) increased drug solubility in buffer shifting the release mechanism toward diffusion.

Moreover, in Table 2, there was no apparent trend for the release exponent (n) change with CP:SA ratio and drug type. As mentioned earlier, CP and SA show similarity in the mechanism of drug release from their matrices regarding the effect of pH and drug solubility. By considering this similarity, the unclear trends of n changing with drug type and CP:SA ratio are probably due to the relatively small and pH-dependent difference in the solubility between the three drugs, and to complication from other factors such as variability in the porosity of matrix tablets due to possible differences in compressibility of

powder blends and in microenvironmental pH due to dissolution of polymers and drug.

The results of ANOVA (Table 3) show that, at 0.05 probability level, only the effect of dissolution medium on release mechanism exponent (n) was significant ($P = 0.003$), and this is in agreement with trends seen in Table 2.

In order to elucidate the suitable ratio for pH-independent release, the similarity factor (f_2) was calculated based on release data in acidic (0.1 N HCl) and buffer (pH = 6.8) media according to the following equation[27]:

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\left(R_t - T_t\right)^2\right]^{-0.5} 100\right\} \quad (5)$$

where R_t and T_t are the amounts dissolved at time t, for the reference and test sample, respectively, and n is the number of samples. According to the US Food and Drug Administration's (FDA) guides for industry[28], an f_2 value greater than 50 (50–100) indicates sameness or equivalence of the two curves and was considered in our study as an indication of pH-independent release.

The results of f_2 comparing the release profiles in the two dissolution media for the three model drugs and for different CP:SA ratios of the matrix former are presented in Table 4. It can be seen that in the case of paracetamol the value of f_2 was higher than 50, indicating pH-independent release, for all CP:SA ratio levels except the lowest (0:100). Since paracetamol has nearly pH-independent solubility and dissolution rate, the pH-dependent release of paracetamol from matrices with low CP:SA level is explained by the remarkable pH-dependent swelling and erosion of SA.

In the case of salicylic acid, $f_2 > 50$ was observed for matrices with CP:SA ratios ≥50:50. This indicates the suitability of matrix tablets with high to medium CP:SA levels for pH-independent release of salicylic acid. The faster swelling of CP in buffer opposes the increase in solubility of salicylic acid and as a result, it helps to minimize the pH-dependent release. The f_2 and K_H results (Tables 2 and 4) indicate the possibility of manipulating the drug release rate, while still being pH-independent, by changing the CP:SA ratio within the ranges 25:75–100:0 and 50:50–100:0 for paracetamol and salicylic acid, respectively.

Table 4. Similarity factor (f_2) comparing the release profiles in 0.1 N HCl (pH = 1.2) and phosphate buffer (pH = 6.8) for three drugs from PM matrix tablets with different CP:SA ratios.

	Similarity factor (f_2)		
CP:SA ratio	Paracetamol	Salicylic acid	Verapamil HCl
0:100	29.6	32.8	40.1
25:75	62.2	34.5	20.5
50:50	70.3	56.8	22.4
75:25	59.1	78.7	21.1
100:0	93.4	59.1	26.8

On the other hand, the results of f_2 were lower than 50 for all CP:SA ratios in the case of verapamil HCl with highest value ($f_2 = 40.1$) found at low CP:SA level, which indicates that the release of verapamil HCl was pH-dependent at all CP:SA ratios but least pH-dependent at the lowest (0:100). The pH-dependence of verapamil HCl release is explained by the remarkably higher solubility of drug, due to higher degree of ionization, in 0.1 N HCl than in phosphate buffer. This property has been opposed by the more constrained release from SA matrix tablets at low pH. However, this opposing effect was not sufficient to achieve pH-independent release, which probably requires the use of a higher SA:verapamil HCl ratio (>1:1). By formulating at about 2:1 polymer:drug ratio, Gutsche et al.[29] were able to achieve pH-independent release for verapamil HCl from SA matrix tablets by using Protanal® LF 240 D, which showed distinctly fast hydration and erosion at higher pH due to relatively LV and high mannuronic

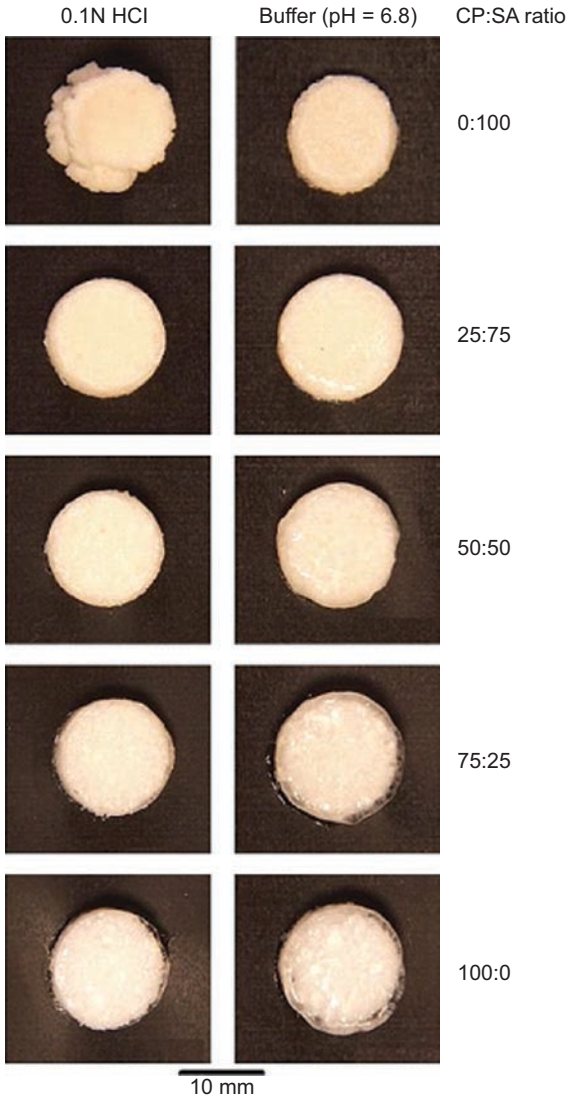

Figure 6. Photographs of paracetamol PM matrix tablets of different CP:SA ratios after immersion for 1 h in 0.1 N HCl and phosphate buffer (pH = 6.8).

acid to guluronic acid (M:G) ratio (viscosity of 1% solution = 75–150 MPa×sec, M:G = 65/35–70/30, molecular weight = 230,000–280,000 g/mol[30]). Also, they found that the addition of fumaric acid enabled pH-independent release of verapamil HCl for alginate grades with less pronounced erosion at higher pH.

Swelling behavior of CP-SA matrix tablets

Swelling and erosion were studied for CP-SA PM matrix tablets containing paracetamol to evaluate their impact on drug release and get further evidence for the drug release mechanism indicated by power law model fitting. The photographs of tablets after 1 h of hydration in the dissolution apparatus (Figure 6) show that the integrity of the matrix tablets of SA was compromised during the test in acidic medium, as evident by the presence of some cracks and lamination. This is consistent with previously reported results and is attributed to the pressure built up within the matrix that could not be released by the matrix swelling[16,31]. All other matrix tablets showed good integrity and it can be seen that the diameter of tablet and thickness of the jelly layer increased by increasing CP:SA ratio and pH of dissolution medium due to decreased erosion (formation of stronger gel network) and increased swelling, respectively.

The results of water uptake and mass loss for matrix tablets with different CP:SA ratio, in two dissolution media and at three time intervals (2, 4, and 6 h) are given in Table 5, and the corresponding results of ANOVA are given in Table 6. Water uptake could not be calculated for three cases of 30 corresponding to matrices with high SA content and long immersion period in buffer due to complete erosion ($W_d = 0$).

Table 5. Results (mean of three replicates[a]) of water uptake and mass loss in two media (0.1 N hydrochloric acid, pH = 1.2, and phosphate buffer, pH = 6.8) at three time intervals for paracetamol PM matrix tablets prepared with different CP:SA ratios.

		Water uptake (%)		Mass loss (%)	
CP:SA ratio	Time (h)	Acid	Buffer	Acid	Buffer
0:100	2	261.0	887.8	37.4	95.2
0:100	4	309.9	—[b]	47.3	100.0
0:100	6	356.8	—[b]	57.0	100.0
25:75	2	101.7	322.2	20.7	33.1
25:75	4	157.6	369.3	30.6	67.5
25:75	6	207.9	—[b]	38.2	100.0
50:50	2	76.8	318.6	8.6	15.2
50:50	4	143.1	409.1	16.8	34.3
50:50	6	171.1	485.7	19.5	51.3
75:25	2	86.8	273.2	5.4	6.9
75:25	4	119.1	483.6	7.8	14.4
75:25	6	191.6	561.9	13.5	26.9
100:0	2	82.4	274.2	0.6	1.1
100:0	4	157.5	457.4	5.1	9.0
100:0	6	242.5	583.3	12.3	19.5

[a]SD ≤59.3 and 12.8 for water uptake and mass loss, respectively.
[b]Complete erosion for tablets occurred.

From the available data in Table 5, it can be seen that water uptake increased with time and it was higher in buffer than in acidic medium. The water uptake at long time of immersion in buffer (6 h) increased with CP:SA

Table 6. ANOVA results for the effect of CP:SA ratio (X_1), dissolution medium (X_2), time (X_3), and two-way interactions on swelling parameters.

	Water uptake[a]		Mass loss	
Effect	*F*	*P*	*F*	*P*
X_1	24.801	0.002	151.013	<0.001
X_2	244.964	<0.001	168.772	<0.001
X_3	23.995	0.003	58.013	<0.001
$X_1 \times X_2$	8.748	0.018	25.071	0.002
$X_1 \times X_3$	0.431	0.861	2.760	0.139
$X_2 \times X_3$	1.763	0.263	5.815	0.050

[a]Missing values were excluded.

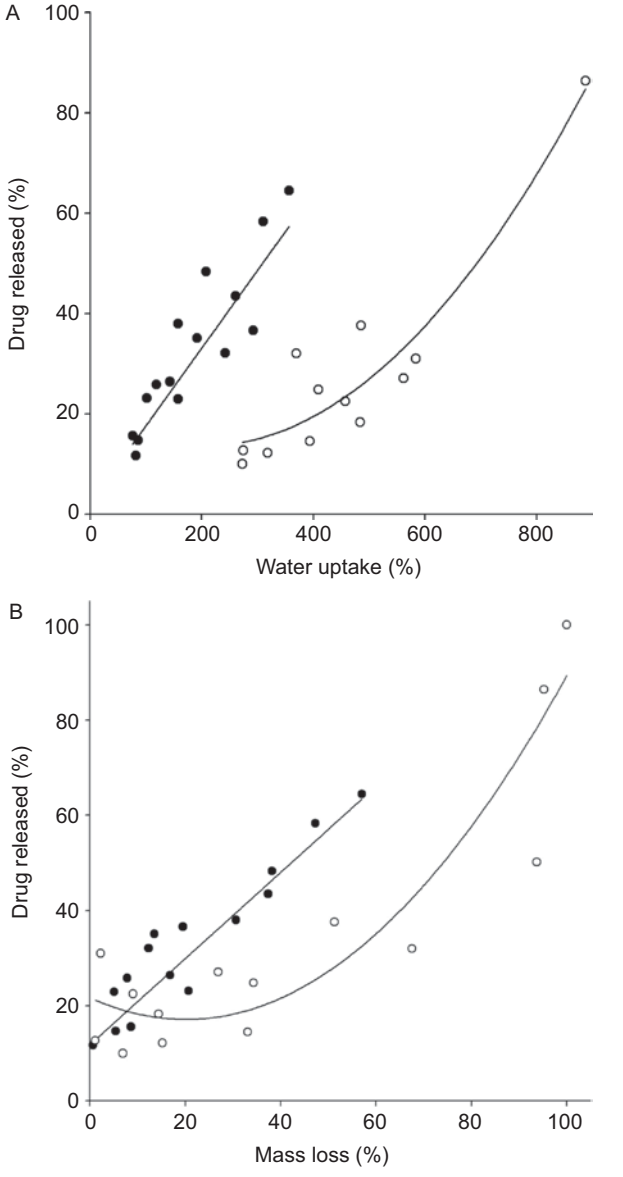

Figure 7. Scatter plots and regression lines of drug released (%) versus water uptake (A) and mass loss (B) in 0.1 N HCl (closed symbols) and phosphate buffer (open symbols) for CP-SA paracetamol PM matrix tablets.

Table 7. Pearson's correlation coefficient, and curve-fitting values (coefficient of determination, R^2, and standard error, SE) for both linear and quadratic models describing the relationship between drug release (%) and swelling parameters in two media (0.1 N hydrochloric acid, pH = 1.2 and phosphate buffer, pH = 6.8) for paracetamol PM matrices prepared using different CP:SA ratios.

			Linear curve fit		Quadratic curve fit	
Swelling parameter	Medium	Pearson's correlation coefficient[a]	R^2	SE	R^2	SE
Water uptake	Acid	0.901	0.811	7.03	0.811	7.32
	Buffer	0.900	0.810	9.39	0.885	7.70
Mass loss	Acid	0.942	0.887	5.45	0.887	5.67
	Buffer	0.886	0.785	15.11	0.830	14.00

[a]Correlation is significant at the 0.01 level (two-tailed).

ratio, whereas at 2 h matrices with low CP:SA level (100% SA) exhibited the highest value of water uptake. This can be explained by faster and more complete swelling and erosion of matrices with high percentage of SA in comparison with those of high CP percentage, which demonstrated slow and gradual swelling due to formation of strong jelly outer layer (seen in Figure 6) that hinders penetration of dissolution medium into the matrix. The change of water uptake with CP:SA ratio was different in the case of acid indicating interaction between CP:SA ratio and dissolution medium. Specifically, the highest values of water uptake in acid were exhibited by matrices of low CP:SA ratio (0:100), whereas the lowest values were exhibited by matrices with 50:50 or 75:25 CP:SA ratio (according to the immersion time). This indicates high capability of the matrix tablets containing SA in the insoluble form, that is alginic acid, to uptake dissolution medium in cracks and pores between insoluble particles due to absence of strong jelly barrier layer, and this is in agreement with previously reported results by Hodsdon et al.[25].

Similarly to water uptake, the mass loss was also higher in buffer than in acidic medium (Table 5), and it increased with time and decreased with CP:SA ratio. It can be seen also from Table 5 that the difference in mass loss between the two media became higher as time increased (except for lowest level of CP:SA) and as CP:SA ratio decreased indicating two-way interactions. The higher swelling and erosion of tablets in buffer than in acid is consistent with the higher release exponent (n) values observed in Table 2.

From Table 6, it can be seen that the main effects of CP:SA ratio, dissolution medium, and time on water uptake and mass loss were highly significant (at probability level of 0.005). The interaction between dissolution medium and CP:SA ratio was also significant for the two parameters (P = 0.018 and 0.002 for water uptake and mass loss, respectively). Also significant (P = 0.050) in the case of mass loss was the interaction, noticed in Table 5, between dissolution medium and time.

Previous reports have established good correlation between swelling parameters and drug release for different hydrophilic matrix formers such as pectin[32], xanthan, karaya, and locust bean gum[33]. By trying in our work to correlate mass loss and water uptake with percent release values at similar time intervals (2, 4, and 6 h), the correlation was weak in the case of water uptake (Pearson's correlation coefficient = 0.478). Better correlation was found for both parameters (with Pearson's correlation coefficient >0.88) when performed for the data corresponding to each medium individually. The relationships were tested for linearity by comparison of linear and quadratic curve fitting on the basis of (1) values of coefficient of determination (R^2) and standard error (SE) and (2) randomness of residuals distribution[17,34]. The results of correlation and curve fitting are presented in Table 7, and the correlation plots are presented in Figure 7 as scatter plots and regression lines that fit better to the data. It can be seen from Figure 7 that the drug release (%) increases with water uptake and mass loss. The R^2 and SE values (Table 7) revealed curvilinearity of relationship with drug release for both swelling parameters in the case of buffer as indicated by better fitting of quadratic models, whereas in the case of acidic medium the relationships were linear as indicated by similarity of R^2 and SE values for quadratic and linear models (which means that there was no superiority of quadratic models). This difference between acid and buffer media in the shape of relationships between swelling parameters and drug release (%) is most probably related to the difference between the two media in kinetics of release, swelling, and erosion of matrix tablets.

Conclusions

Matrix tablets based on CP and SA form a potentially useful versatile system for pH-independent controlled release that can be prepared via SD technique and more simply by direct compression of physical mixtures. The processing method (SD or PM) markedly affected drug release from matrix tablets. By changing the CP:SA ratio in the matrix tablets, it is possible to control the rate and reduce pH-dependence of drug release.

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Declaration of interest

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