The Effect of Sodium Alginate on Physical and Dissolution Properties of Surelease®-Matrix Pellets Prepared by a Novel Pelletizer

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The aim of this study was to investigate the effect of sodium alginate on the physical and dissolution properties of Surelease®-matrix pellets prepared by a novel pelletizer-equipped piston extruder and double-arm counter-rotating rollers. The mean values of the shape factor (e_R) and the aspect ratio of Surelease®-matrix pellets were 0.615—0.625 and 1.06—1.070, respectively, indicating good sphericity of the pellets. The drug release rate increased as the amount of sodium alginate increased due to hydration, swelling, and erosion within the Surelease®-matrix pellets. In addition, the porosity of pellets also increased with increasing sodium alginate content. The results of this study show that sodium alginate has a greater effect on the drug release rate than the drug release mechanism within the Surelease®-matrix for sparingly water-soluble drug, such as tamsulosin hydrochloride.

Key words pellet; Surelease®; sodium alginate; dissolution

Ethylcellulose is an inert hydrophobic polymer that has been studied extensively as a matrix forming material or coating material for controlled drug delivery systems. Ethylcellulose has been used in the powder state for direct compression or in a granular form as aqueous dispersion for matrix formation. The mechanism of drug release from an inert porous matrix granulated with aqueous ethylcellulose dispersion appears to be diffusion,[1,2] and the release rate is influenced by coexcipients such as plasticizers, organic acid, and lactose within the matrix of these pellets or tablets.[3,4]

In a previous study, we successfully prepared pellets using a novel pelletizer comprising a ram extruder and modified double arm counter-rotating roller[5—7] and demonstrated that Surelease® and sodium alginate are useful excipients in the preparation of tamsulosin hydrochloride controlled release pellets.[6] In this study, the effect of sodium alginate on the physical properties of Surelease®-matrix pellets was investigated by a characterization of the size, shape, friability, porosity, and density of pellets. The effect of sodium alginate on hydration, erosion and drug release from Surelease®-matrix pellets was also investigated.

Experimental

Materials Poloxamer 407 (Lutrol® F127, BASF, Germany), microcrystalline cellulose (Avicel™ PH102, FMC, U.S.A.), sodium alginate (Duckalgin® NSPH, Kibun Food Chemica, Japan), and Surelease® (E-7-19010, Colorcon, U.S.A.) were used. Tamsulosin hydrochloride was purchased from Youn Sung Fine Chemicals Co., Ltd. (99.6% purity, Korea). All organic solvents were of HPLC grade. All other chemicals were of reagent grade.

Preparation of Pellets The formulations of the pellets are shown in Table 1 and the total mass for each batch is 602.8 g. Briefly, tamsulosin hydrochloride (0.2 mg/capsule) was used as a model drug and was dissolved with poloxamer 407 in distilled water. The drug/surfactant solution was uniformly mixed with microcrystalline cellulose (120—280 g), sodium alginate (0—160 g), and magnesium trisilicate (160 g) at 60 rpm for 20 min. The mixture was then kneaded in a mixer (Kitchen Aid Inc., MI, U.S.A.) with Surelease® diluted in distilled water at 100—120 rpm for 30 min. The Surelease®-matrix pellets were prepared using a novel pelletizer-equipped piston extruder and double-arm counter-rotating rollers (Fig. 1) as previously reported.[5—7] The wet mass of drug/excipients (approximately 100 g) was extruded using an oil pressure-extruding machine (3″ motor 2 p, 1/2 hp, Changsung Industry, Korea) and a piston extruder consisting of a hollow steel cylinder containing a sliding steel piston, at a constant speed of 250 mm/min. The length of the die was 10 mm and the diameter 1.2 mm. The extrudates were put into double-arm counter-rotating rollers (3″ motor 2 p, 1/2 hp, Changsung Industry) with different speeds for the upper (160

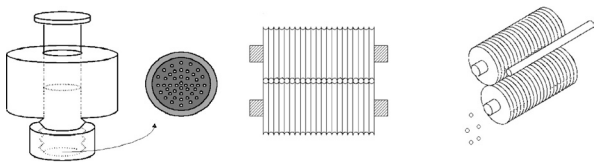

Fig. 1. Experimental Apparatus Used in the Extrusion/Pelletization Process, Showing the Piston Extruder (Left) and Double-Arm Counter-Rotating Rollers (Middle and Right)

These two rollers had continuous semicircular pits of constant diameter between projected lines along the plate of the roller and vertically to the axis of rotation. The rollers closely contacted each other and rotated in reverse. When the cylindrical strand was put into the osculating plane of the two rollers parallel to the axis of rotation, the strand was revolved by the two rollers, which counter-rotated at different speeds of 160 rpm (upper) and 80 rpm (lower). Subsequently, the strand was cut off by the projected lines and compressed by the semicircular pits. As a result, the cylindrical strand was formed into spherical pellets with constant diameters.

Table 1. Formulations of the Surelease®-Matrix Pellets

Formulations	Tamsulosin HCl	Poloxamer 188	Sodium alginate	Avicel PH102	Magnesium trisilicate	Surelease® (by solid)
F1	0.2	0.5	0	70	40	40
F2	0.2	0.5	10	60	40	40
F3	0.2	0.5	20	50	40	40
F4	0.2	0.5	30	40	40	40
F5	0.2	0.5	40	30	40	40

All quantities given in mg.

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rpm) and lower (80 rpm) rollers. The cylindrical strand was shaped into spherical pellets with uniform diameter, and the pellets were dried in a 60 °C drying oven until their weight remained constant.

Friability Test The friability test was conducted by rotating 10 g of pellets with 10 g of glass beads in a PTFR-A friability tester (Pharma Test, Germany) at 25 rpm for 10 min.[7]

Image Analysis of Pellets The size, aspect ratio, and shape factor[8] (e_R) of pellets were determined using a video microscope system (Alphasystech, Korea) equipped with a Sony model Super HAD CCD camera (Tokyo, Japan) and ITPro 3.03 image analysis software (Sometech Inc., Korea).[6,7] The size of the pellets was estimated as a mean Feret diameter obtained from four different angles. The aspect ratio is defined as the ratio between the longest Feret diameter and the Feret diameter perpendicular to this measure. The shape factor (e_R) was calculated according to:

$$e_R = \frac{2\pi}{\text{perimeter}} \frac{r_e}{f} - \sqrt{1 - \left(\frac{\text{breadth}}{\text{length}}\right)^2} \quad (1)$$

where r_e is the mean radius derived from a mean Feret diameter obtained from four different angles, and f is a correction factor[8]:

$$f = 1.008 - 0.231\left(1 - \frac{\text{breadth}}{\text{length}}\right) \quad (2)$$

At least 100 pellets of each formulation were counted.

Micrometric Properties Total pore surface area, bulk and apparent density, and porosity of the pellets were determined by mercury intrusion porosimetry (AutoPore IV 9500, Micromeritics, U.S.A.). Total pore area (A_{tot}) was calculated as follows:

$$A_{tot} = \frac{1}{\gamma \cos\theta} \int_0^{V_{tot}} P \cdot dV \quad (3)$$

where P is the pressure (psia), V is the intrusion volume (ml/g), and V_{tot} is the total specific intrusion volume (ml/g). Envelope (bulk) density (ρ_{se}) of the pellets was calculated as follows:

$$\rho_{se} = \frac{W_s}{V_P - V_{Hg}} \quad (4)$$

where W_s is the weight of the pellet sample (g), V_p is the empty penetrometer (ml), and V_{Hg} is the volume of mercury (ml).
Apparent (skeletal) density (ρ_{sa}) of pellets was calculated as follows:

$$\rho_{sa} = \frac{W_s}{V_{se} - V_{tot}} \quad (5)$$

where V_{se} is the volume of the penetrometer minus the volume of the mercury (ml).
Finally, the percent porosity of the pellets was calculated as follows:

$$\text{porosity (\%)} = \left(1 - \frac{\rho_{se}}{\rho_{sa}}\right) \times 100 \quad (6)$$

Mercury contact angle, surface tension, and density were taken as 130°, 485 dyn/cm and 13.5389 g/ml respectively.

Scanning Electron Microscopy The morphology of pellet surfaces and pellet cross sections were examined by scanning electron microscopy (SEM; JSM-7000F, Jeol Ltd., Japan).

Dissolution, Hydration and Erosion Studies The drug release from Surelease®-matrix pellets was measured according to the USP XXVIII basket method using a dissolution apparatus (Vankel VK7000, Cary, NC, U.S.A.). The dissolution medium was 900 ml of intestinal fluids (pH 6.8), which was kept at a constant temperature of 37±0.1 °C, with the baskets rotating at 50 rpm. At defined time intervals, 5 ml samples were withdrawn and replaced with an equal volume of fresh dissolution medium. The samples were analyzed using HPLC as described in the previous study.[6,9] Hydration and erosion of pellets were also determined under conditions identical to those described for the dissolution testing. At predetermined times, the hydrated pellets were carefully removed from the dissolution medium and tapped gently with tissue paper to remove excess surface water. After determining the wet weight, pellets were dried at 60 °C until their weight was constant, and weighed again to determine the remaining dry weight. Hydration and erosion of pellets were determined gravimetrically according to the following equations:

$$\text{hydration (\% water uptake)} = (\text{wet weight} - \text{original dry weight})/\text{original dry weight} \times 100 \quad (7)$$

$$\text{erosion (\% mass loss)} = (\text{original weight} - \text{remaining dry weight})/\text{original weight} \times 100 \quad (8)$$

Statistical Analysis The effect of sodium alginate on the properties of pellets was evaluated using a one-way analysis of variance (ANOVA) (SPSS 12.0). $p<0.05$ was considered to be statistically significant.

Results and Discussion

Physical Properties of Pellets Drug content in pellets was determined by the method described in the previous study[6] and was found to be between 98.9% and 101.2% as expected. The mean diameter of pellets ranged from 1240—1265 μm, indicating no significant difference in pellet size ($p>0.05$). The mean values for the shape factor and aspect ratio of matrix pellets ranged from 0.615 to 0.625 and from 1.061 to 1.070, respectively (Table 2). These values demonstrated that the matrix pellets were spherical independent of the amount of sodium alginate ($p>0.05$). Generally, the theoretical value is 1.0 for both shape factor (e_R) and aspect ratio, and 0.6 and 1.1 are recommended as limiting values that indicate good sphericity for the shape factor (e_R) and aspect ratio, respectively.[8] Therefore, the matrix pellets prepared using this novel pelletizer were morphologically satisfactory, with no significant difference in pellet size or shape.

Table 3 shows the micrometric properties of the pellets. The porosity of pellets gradually increased with increasing

Table 2. Size and Shape of the Surelease®-Matrix Pellets

Formulations	Size[a,c] (μm)	Aspect ratio[b,c]	Shape factor[b,c] (e_R)
F1	1245±1.075	1.067±0.039	0.622±0.053
F2	1261±1.093	1.070±0.045	0.621±0.077
F3	1240±1.091	1.063±0.041	0.625±0.052
F4	1255±1.123	1.061±0.033	0.622±0.050
F5	1265±1.122	1.063±0.040	0.615±0.064

a) Geometric mean diameter (d_g)±geometric standard deviation (σ_g). *b*) Mean± standard deviation. *c*) No significant differences between all formulations ($p>0.05$).

Table 3. Friability, Total Pore Area, Bulk, Apparent Density, and Porosity of the Surelease®-Matrix Pellets

Formulations	Friability (%)	Total pore area[a,b] (m^2/g)	Bulk density[a,b] (g/ml)	Apparent density[a,b] (g/ml)	Porosity[a,c] (%)
F1	0.57	21.39±2.04	1.26±0.06	1.51±0.08	16.38±0.90
F2	0.65	21.48±1.57	1.28±0.05	1.53±0.07	16.54±0.86
F3	0.60	20.57±4.40	1.19±0.01	1.43±0.01	16.99±0.53
F4	0.89	20.39±1.23	1.24±0.07	1.51±0.09	17.83±0.73
F5	0.87	21.47±0.92	1.25±0.01	1.54±0.03	18.86±0.69

a) Mean±standard deviation ($n=3$). *b*) No significant differences between all formulations ($p>0.05$). *c*) Significant differences between F5 and F1, and between F5 and F2 (Tukey HSD test, $p<0.05$).

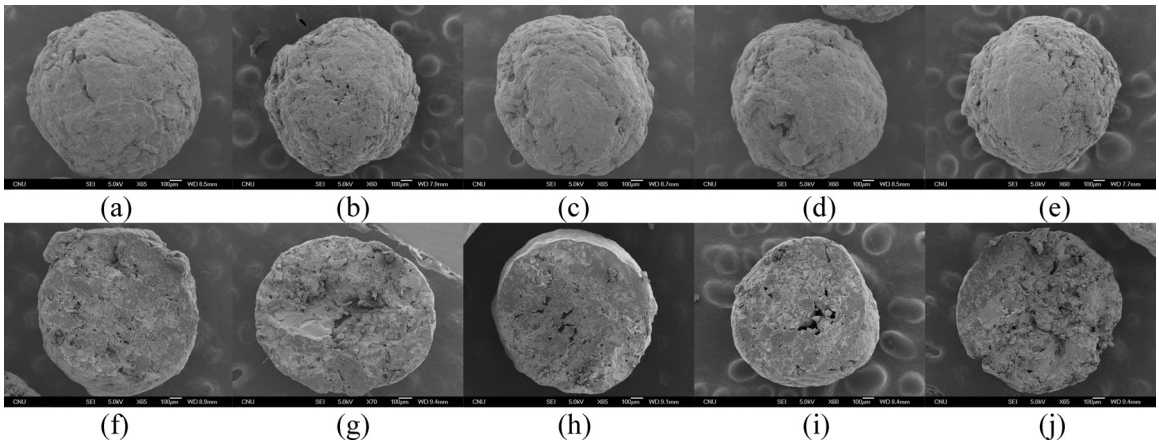

Fig. 2. Scanning Electron Microscopy Images of the Surelease®-Matrix Pellets (a) F1, (b) F2, (c) F3, (d) F4, (e) F5
Images (f), (g), (h), (i) and (j) are cross sections of (a), (b), (c), (d) and (e), respectively.

sodium alginate content. In addition, the same pores and channels were apparent on the surface of pellets in SEM images (Fig. 2). It is postulated that the porosity of pellets is due to the nature of sodium alginate/microcrystalline cellulose, which swells in contact with water during preparation of the pellets, particularly in the kneading, extrusion, and pelletization processes, and is porous when water inside and on the surface of the pellets is removed during the drying process. However, there were no significant differences in total pore area, bulk density, and apparent density of pellets ($p>0.05$). Furthermore, the friability (%) of Surelease®-matrix pellets tested with glass beads was below 1% for all formulations, indicating good hardness and high quality.

Dissolution, Hydration and Erosion Studies The dissolution profiles are presented in Fig. 3. Four models (Zero-order, Hixon–Crowell, Higuchi, and Korsmeyer–Peppas) were applied to these profiles in order to understand the drug release rate and mechanism in the pellet (Table 4). The optimum values for the parameters presented in each equation were determined by nonlinear regression using SPSS 12.0 software (SPSS, Chicago, IL, U.S.A.). As shown in Table 4, dissolution data of the pellets were well fitted according to the zero-order model and Korsmeyer–Peppas model.

As shown in Fig. 3a, the drug release profiles were significantly affected by sodium alginate. Analysis of variance showed that there are significant differences among the formulations ($p<0.05$), which were ranked by the Student–Newman–Keuls test in order of increasing drug release rate (obtained from the zero-order model) as follows: 0%< 6.6%<13.3%<19.9%<26.5% with respect to % sodium alginate. Thus, the drug release rate gradually increased as the amount of sodium alginate increased (Fig. 4). In general, drug release is critically influenced by the hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer.[10] Visual observation indicated that all matrix pellets swelled, eroded, and subsequently disintegrated in dissolution medium during the dissolution test (1.5—4 h), whereas the matrix pellets without sodium alginate (F1) remained intact for at least 4 h.

Gravimetric evaluation of hydration and erosion (mass loss) revealed that the rate and extent of water uptake were significantly affected by the sodium alginate content. As shown in Fig. 3, there is an initial rapid uptake of water by

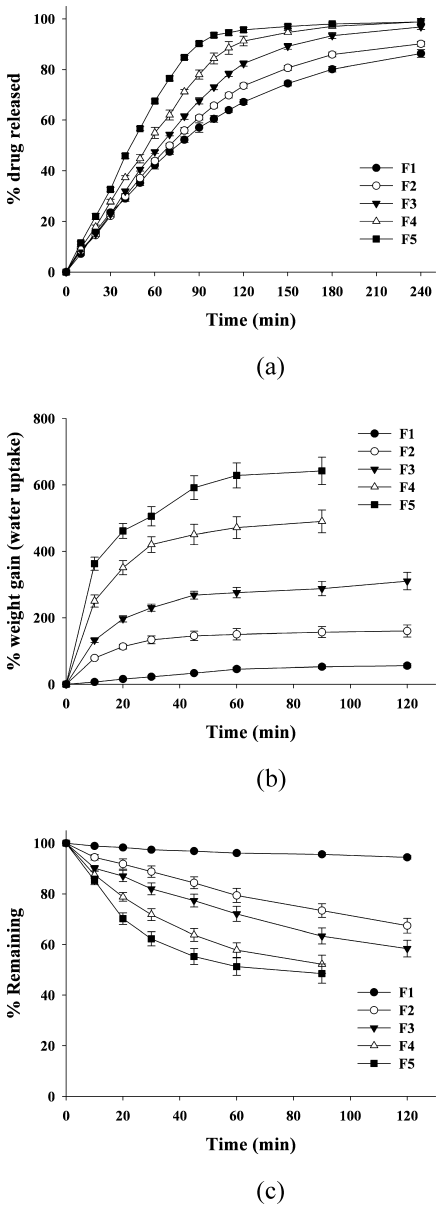

Fig. 3. The Effect of Sodium Alginate on Dissolution (a), Hydration (b; Showing % Water Uptake) and Erosion (c; Showing % Pellet Remaining, Calculated as 100% Mass Loss) of the Pellets

Table 4. Mathematical Models and Statistical Analyses Applied to the Dissolution Profiles

Model[a)]	Statistics[b)]	F1	F2	F3	F4	F5
Zero-order	R^2	0.9702	0.9912	0.9964	0.9988	0.9981
	k	6.56×10^{-3}	7.08×10^{-3}	7.88×10^{-3}	9.14×10^{-3}	1.13×10^{-2}
	S.E.	1.51×10^{-4}	9.04×10^{-5}	6.81×10^{-5}	6.31×10^{-5}	1.08×10^{-4}
Hixon–Crowell	R^2	0.9985	0.9960	0.9875	0.9882	0.9790
	k	2.73×10^{-3}	2.91×10^{-3}	3.13×10^{-3}	3.63×10^{-3}	4.51×10^{-3}
	S.E.	1.89×10^{-5}	3.61×10^{-5}	7.78×10^{-5}	9.41×10^{-5}	1.75×10^{-4}
Higuchi	R^2	0.8852	0.8500	0.8116	0.8113	0.7913
	k	5.45×10^{-2}	5.56×10^{-2}	5.47×10^{-2}	5.91×10^{-2}	6.69×10^{-2}
	S.E.	2.60×10^{-3}	3.40×10^{-3}	4.40×10^{-3}	5.09×10^{-3}	6.74×10^{-3}
Korsmeyer–Peppas	R^2	0.9918	0.9980	0.9958	0.9988	0.9984
	k	9.73×10^{-3}	9.64×10^{-3}	8.81×10^{-3}	9.82×10^{-3}	1.13×10^{-2}
	S.E.	1.11×10^{-3}	5.74×10^{-4}	8.90×10^{-4}	5.74×10^{-4}	8.55×10^{-4}
	n	0.91	0.93	0.97	0.98	1.00
	S.E.	2.93×10^{-2}	1.57×10^{-2}	2.83×10^{-2}	1.69×10^{-2}	2.28×10^{-2}

a) Zero-order: $M_t/M_\infty=kt$, Hixon–Crowell: $M_t/M_\infty=1-(1-kt)^3$, Higuchi: $M_t/M_\infty=k\sqrt{t}$, Korsmeyer–Peppas: $M_t/M_\infty=kt^n$, where $M_t/M_\infty=$ is the fraction of drug released up to time t and k is the kinetic constant. For comparison, only the points within the interval $M_t/M_\infty\leq0.6$ were used. *b*) R^2, determination coefficient: S.E., standard error of parameters k and n.

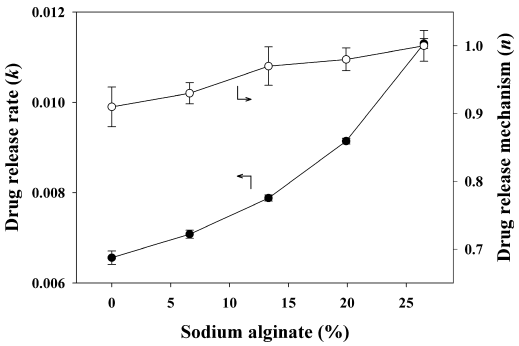

Fig. 4. The Effect of Sodium Alginate on the Drug Release Rate (k; Obtained from Zero-Order Model), and drug Release Mechanism (n)

●, Drug release rate (k); ○, drug release mechanism (n).

the dry pellets during the first 20—60 min, followed by stabilization of the wet weight due to the increasing rate of erosion. The erosion of pellets increased with increasing sodium alginate content within Surelease®-matrix pellets. After 120 min the weight gain of the pellets without sodium alginate (F1) was only 55%, whereas that of the pellets containing 26.4% sodium alginate (F5) was 642%. Furthermore, erosion (mass loss) of the pellets without sodium alginate (F1) was only 5.6%. Therefore, it is likely that the drug release rate was influenced by hydration and swelling of sodium alginate within Surelease®-matrix pellets, and by pellet erosion.

As shown in Fig. 4, the drug release mechanism (n) values gradually increased with increasing sodium alginate content. However, the drug release mechanism (n) values of Surelease®-matrix pellets ranged from 0.91 to 1.00, indicating zero-order transport.[11,12] Therefore, sodium alginate affects the drug release rate more than the drug release mechanism within the Surelease®-matrix for sparingly water-soluble drug, such as tamsulosin hydrochloride.

Conclusion

The mean values of the shape factor (e_R) and the aspect ratio of Surelease®-matrix pellets prepared using a novel pelletizer were 0.630—0.659 and 1.051—1.063, respectively, indicating good sphericity of pellets. There were no significant differences among pellets with respect to size and shape. Furthermore, the drug release rate gradually increased as the amount of sodium alginate increased due to hydration, swelling, and erosion within the Surelease®-matrix pellets.

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