Journal of Pharmaceutical Investigation
Vol. 41, No. 2, 83-90 (2011)

Evaluation of Physical Properties as Magnesium Stearate Blended in Hydrophilic Matrix Tablets

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(Received March 16, 2011 · Revised March 29, 2011 · Accepted April 4, 2011)

ABSTRACT – Main objectives of this study were to investigate the effects of a lubricant, magnesium stearate, as blended in a hydrophilic matrix tablet and to identify significant factors using a tablet ejection force and a swelling property. The characteristics of tablet ejection were evaluated with three different compression forces (30, 40, and 60 MPa) and two controlled factors, amount of magnesium stearate and its mixing time. A hydrophilic model drug (terazosin HCl dihydrate) was regarded as a default factor. Tablet swelling was also evaluated. The optimal amount of PEG compared to PEO was set to be 88.50% w/w. As the amount of magnesium stearate was varied from 0.79% to 2.20% w/w, the amount of PEO and PEG was adjusted to meet the tablet's total weight while maintaining the ratio between the two excipients constant. As the mixing time of magnesium stearate was increased, the tablet ejection force and the swelling property were decreased. As the amount of magnesium stearate was increased, the tablet ejection force and the swelling property were decreased since the increased mixing time and the amount of magnesium stearate induced hydrophobic properties of the matrix tablet more effectively. The ejection force of the tablet increased as a result of increase in the compression force, which means that the breaking of tablet/die-wall adhesion energy was also increased when the compression energy was increased. The results gave a valuable guide how to choose suitable amount of the lubricant with processing conditions for the development of hydrophilic matrix formulations.

Key words – Lubricant, Ejection force, Matrix tablet, Swelling kinetics, Hydrophilic swellable polymer

Most tablet formulations include some additives with a purpose of reducing the inter-granular and die wall friction. They are called lubricants and regarded as one of the critical ingredients in tablet formulations. They need to have low shear strength but be cohesive perpendicular to shear plane to perform their function decently (Marshall, K., 1976).

As one of the most common lubricants, magnesium stearate, can aid the compaction process by reducing the wall friction during ejection from a tablet compression (Sheskey et al., 1995), improving powder flow (Podczeck and Miah, 1994), increasing bulk powder density (Dansereau and Peck, 1987; Shah and Mlodozeniec, 1977), and reducing the potential of the pharmaceutical formulation to adhere on exposed metal surfaces during compaction process (Sabir et al., 2001; Yamamura et al., 2009). However, it still has some issues on tablet properties including tablet strength, disintegration time, and dissolution rate (Asker et al., 1973; van der Watt, 1987). The restrictive effects were dependent on the lubricant's concentration and its mixing time in the formulation (Bolhuis et al., 1987). These effects were more pronounced with extended mixing (van der Watt, 1987; Shah et al., 1977), mainly due to the lubricant film formation during the process (Johansson, 1986); magnesium stearate molecules can be sheared off mechanically during mixing and the sheared particles adhere to the ingredients forming a film. This film can interrupt particles binding together during compression and water uptake of the tablet. A short mixing time may bring about poor distribution of magnesium stearate, which does not impair the efficiency of the lubricant. Therefore, the brief mixing time has been applied often when magnesium stearate is blended with other tablet ingredients (Kikuta et al., 1994).

Matrix tablets are the most popular method of oral drug administration and hydrophilic swellable polymers have been used widely in the matrix formulations to modify and/or modulate drug release rate (Alderman et al., 1984; Ford et al., 1991; Juarez et al., 2001; Rao et al., 1990). The main purpose of the matrix system is to extend drug release profiles to maintain a constant *in vivo* plasma drug concentration (Ebube and Jones, 2004; Madhusudan Rao et al., 2001; Neau et al., 1999; Nerurkar et al., 2005). A large number of formulation

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DOI : 10.4333/KPS.2011.41.2.083

factors, including the physicochemical properties of the components, their compositions and ratios in the formulations, and manufacturing process parameters can influence the drug release behavior from the final drug products (Mitchell et al., 1993; Gao et al., 1996; Campos-Aldrete and Villafuerte-Robles, 1997).

Compared to the other pharmaceutical materials, only a little amount of lubricants is usually used, but this handful amount may have a significant effect on manufacturing process and physical properties of the matrix tablet. For example, when a hydrophilic matrix comes into contact with water, the pores near the surface of the matrix can be filled with water and the drug release is initially controlled by the dissolution of the drug in the water-filled pores and by its diffusion in water (Korsmeyer et al., 1983). In this process, as hydrophilic polymers are coated with the hydrophobic lubricant, wetting or water penetration of inner side of matrix tablet might be limited. Thus, the drug release and swelling kinetics of matrix tablet can be affected by the excipient.

The main purpose of the present study was to evaluate the effects of a lubricant, magnesium stearate, when blended with a hydrophilic matrix tablet and to control factor levels (mixing time and amount) using the density, the ejection force, and the swelling property. The hydrophilic matrix tablets are mainly composed of PEO (polyethylene oxide) and PEG (polyethylene glycol). The characteristics of tablet ejection force were evaluated with three different compression forces (30, 40, and 60 MPa). The characteristics of tablet swelling property were evaluated with two different factors, the amount of magnesium stearate and the mixing time. Terazosin was used as a hydrophilic model drug and also regarded as a default factor.

Materials and Methods

Materials

The model drug, terazosin HCl dihydrate, was purchased from Hanseo Chemical (Seoul, Korea). PEO (Polyox WSR-303) of average molecular weight 7.0×10^6 (mean particle size 150 μm) was obtained from Dow Chemical (Midland, MI, USA). Polyethylene glycol 6000 (PEG 6000) was purchased from Sanyo Chemical Industries (Ibaraki, Japan). Magnesium stearate was purchased from Faci Asia (Jurong Island, Singapore). All other reagents were of analytical or HPLC grade and used as received.

Preparation of matrix tablets

The formulations of each tablet are shown in Table 1; PEO is a gel-forming agent and PEG is a gel-enhancing agent which facilitates water absorption into the tablets. The relative amount of PEO and PEG has an effect on the swelling rate, mechanical strength of the viscous-gel, and also release rate. In our previous study, optimal amount of PEG compared to PEO was suggested to be 88.50% w/w (Park et al., 2010). The amount of magnesium stearate varied from 0.79% to 2.20% compared to the tablet's total amount. As the amount of magnesium stearate increased, the amount of PEO and PEG is adjusted to meet the total tablet's weight while maintaining the ratio between the two excipients constant.

All materials of the formulations were passed through a sieve (#40 mesh) to remove any aggregates before mixing. The model drug (terazosin HCl dihydrate) was mixed with PEO and PEG manually in a mortar. In order to blend with magnesium stearate, the previous powder mixture was transferred to stainless steel V-mixer (Kopamtec, Anyang, Korea) with a volume of 1000 cm^3, whose fill-weight was about 12% of the mixer volume. The magnesium stearate was added into the V-mixer and then rotated at 60 rpm in predetermined time intervals. The resulting mixture was compressed on a single punch Carver Laboratory Press (Carver Inc., Wabash, IN, USA) using plane-faced punches with a diameter of 12.0 mm. The total weight of each tablet was around 241 mg. The dimensions were measured with a digital slide caliper (Mitutoyo Corp., Kawasaki, Japan).

Ejection force measurement

The tablet ejection profile, essentially the continuously measured force necessary to push the tablet out from the die, includes the manifestation of the wall friction during ejection. Low ejection forces are preferred in order to minimize equipment wear and tabletting defects. High ejection forces are normally associated with tabletting problems such as tablet seizure within the die that may cause equipment damages and tabletting defects (Anuar and Briscoe, 2009). The ejection forces could be measured with a Texture analyzer (TA. XT Express, Stable Micro Systems, Godalming, UK). The analysis parameters were as following:

- Test mode : compression
- Test speed : 1.0 mm/s
- Target mode : Distance
- Distance : 20.0 mm
- Trigger Type : Button
- Stop Plot At. : Start position
- Target mode : Auto

Density measurement

The true density was determined using a helium pycnometer

(AccuPyc 1330, Micromeritics Instrument Inc., Norcross, GA, USA). The accuracy of the pycnometer was evaluated using a standard steel sphere before measurements on a series of samples. The experimental sample was accurately weighed and loaded into the sample cell. The sample volume was computed by measurements of the pressure observed by filling the sample chamber with helium gas followed by discharging the gas into a second empty chamber. The measurements were repeated for 5 cycles.

The bulk and the tap densities were determined by MT-1000 (Seishin Enterprise Co., Tokyo, Japan). The bulk density was determined after dropping powder at 100 ml mass cylinder using the MT-1000. The tab density was determined after 2,000 taps. Each analysis was repeated in triplicate.

The increase in the density of powders is related to their cohesiveness. Ratios of the poured to tapped densities are expressed in two ways to provide indices of flowability.

Hausner Ratio = (tapped density)/(poured bulk density)

Compressibility (Carr Index) = (100×(tapped density-poured bulk density))/(poured bulk density)

The Hausner Ratio varies from about 1.2 for free-flowing powders to 1.6 for cohesive powders. The Carr Index classifications are listed in 5-12% (free flowing), 12-16% (good flow), 18-21% (fair flow), 23-35% (poor flow), 33-38% (very poor flow), and above 40% (extremely poor) (Davies et al., 2004).

Evaluation of tablet gelation

Gelation index is a useful means to represent the portion of a tablet that has undergone gelation in time. Each tablet was inserted between two transparent polyacrylate plates (5 cm × 5 cm) and held tight with a rubber band. The tablet and polyacrylate plates were immersed in 900 mL of dissolution medium (pH 6.8, 37°C) and stirred with a magnetic bar (300 rpm/min). Test tablets were removed from the medium at predetermined time intervals (30, 60, 90, 120, 150, 180, 240, and 300 min) and the diameters of the gelated tablets were measured with a caliper. After the gel layer was carefully peeled off, the diameter of the non-gelated core was also measured (D_{obs}). The gelation index was calculated using the following equation (Sako et al., 1996).

$$Gelation\ Index\ (G,\ \%)\left\{1-\frac{(D_{obs})^3}{(D_{ini})^3}\right\}\times 100$$

D_{obs} : diameter of the portion not gelled after the test

D_{ini} : diameter of the tablet before the test

Results and Discussion

Among the excipients in Table I, magnesium stearate might affect physical properties mainly due to its hydrophobic nature. It is added to tablet formulations primarily to reduce friction between the die wall and granules as the tablet is formed and ejected (Sprowl, 1974; Lachman et al., 1970). Additionally, swelling and dissolution rates were dependent on the amount of magnesium stearate and its processing condition (Iranloye and Parrott, 1978; Shah and Mlodozeniec, 1977). Therefore, it is important to control the amount of magnesium stearate in each formulation with relevant processing conditions. Its maximum and minimum amounts were selected in advance based on our previous experience and the extremes were ruled out as shown in the Table I (0.79~2.20% w/w).

Tablet ejection force and gelation were conducted with two factors x_1 and x_2: one was the amount of magnesium stearate and the other was a mixing time, respectively. The amount of model drug was fixed as shown in the table due to its expected pharmacological effect. While maintaining the ratio between the PEO and PEG, the total amount of the both excipients was adjusted according to the changed amount of magnesium stea-

Table I. *Components of the matrix tablets with two controlled factors: the amount of magnesium stearate (x_1) and mixing time (x_2). The API (terazosin) is regarded as a default factor*

Run order	API	Excipients		Controlled factors x_1		x_2
	Terazosin (g)	PEO (g)	PEG (g)	Mg stearate (g)	% Amount	Mixing time (min)
1	2.97	60.99	53.98	2.66	2.20	7.00
2	2.97	61.76	54.66	1.21	1.00	10.00
3	2.97	61.44	54.38	1.81	1.50	2.76
4	2.97	61.13	54.09	2.41	2.00	10.00
5	2.97	61.90	54.78	0.96	0.79	7.00
6	2.97	61.44	54.38	1.81	1.50	11.24

rate so that the total amount of a tablet could be maintained.

Physical properties of the powder in the experimental runs

The bulk, tapped, and true densities for the mixed powder from the formulations in Table I were measured and listed in Table II. Since the true density might be dependent mainly on the components of the materials, there was no significant difference in true densities among the formulations (1.23~1.26 g/mL).

The flowability can be evaluated using powder properties such as density, surface area, moisture content, particle shape, particle size, and size distribution. Among the many methods available, Carr index have been used widely to get a rough idea on the flow properties. Generally, directly compressible materials may have a good flowability due to their additional manufacturing processes for the improvement of powder properties like spray drying, spheronization, formation of aggregation, and so on. However, in this experiment, the powder showed poor flowability (33~59%) and it was difficult to draw any significant effects which factor might have (x_1 or x_2).

Table II. *Various densities and Carr index of the mixed powder from the formulations in Table I*

Run order	Density (g/mL)			Carr index
	Bulk	Tapped	True	
1	0.48±0.00	0.67±0.00	1.25±0.00	39.58
2	0.49±0.00	0.65±0.00	1.25±0.00	32.65
3	0.50±0.01	0.67±0.00	1.25±0.00	34.00
4	0.45±0.01	0.68±0.00	1.26±0.00	51.11
5	0.44±0.01	0.70±0.00	1.25±0.00	59.09
6	0.45±0.00	0.66±0.00	1.23±0.00	46.67

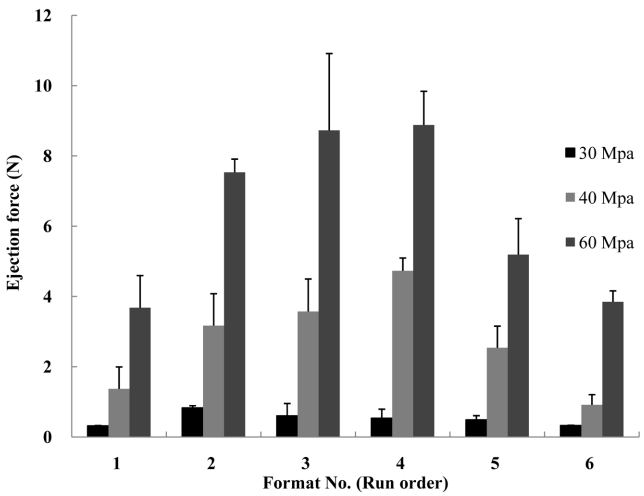

Figure 1. Tablet ejection force of the formulations tested in this study. Different compression force was adopted using 30, 40, and 60 MPa. The bars were the ejection force of 30, 40, and 60 MPa compression force, respectively (from left to right).

Measurement of tablet ejection force

In order to investigate the effects of various levels of magnesium stearate as well as its mixing time on the tablet ejection force, the upper and the lower punches were removed carefully after compression at first. Then, the die, holding compressed matrix tablet, was transferred to the bottom plate of the Texture analyzer. Finally, the probe from the instrument measured the force to push the tablet out from the die. The ejection profile, essentially the continuously measured force necessary to push the tablet out from the die, includes the manifestation of the wall friction during ejection (Anuar and Briscoe, 2009).

As shown in Figure 1, the ejection force of the compressed tablets increased with increasing compression force. Increasing the amount of magnesium stearate and decreasing the mixing time lowered ejection forces at the experimental scope. Moreover, sticking to the die wall was not observed in any of the experimental runs. The degree of the increase for the ejection force with the matrix tablet as increasing compression force was large at Run order 3 and 4 and was small at Run order 1 and 6. The ejection force in Run order 1 and 6 was 0.32 N and 0.33 N at 30 MPa (compression force) and 3.68 N and 3.85 N at 60 MPa (compression force), respectively. Run order 1 had a largest amount of magnesium stearate (2.20 w/w%) with a mixing time of 7.00 minute. On the other hand, Run order 6 had a longer mixing time of 11.24 minute with the amount of magnesium stearate 1.50 w/w%. Powders from the Run order of 1 and 6 were covered with lubricants more efficiently compared to the other experimental runs. As the mixture proceeds, magnesium stearate continues to shear off and coat adjacent particles of the experimental powder. The higher the amount of magnesium stearate is used and/or the longer the mixing time continues, the more complete of the coating of the adjacent particles will be formed. Magnesium stearate of covered powder surface provides a film that will prevent solid-to-solid contact, and will easily be sheared (Jentgen, 1971).

Run order 1 and 5 had the same mixing time of 7.00 minutes but different amounts of magnesium stearate: Run order 1 contained 2.20 w/w% and Run order 5 contained 0.79 w/w%. The ejection force of the Run order 1 and 5 was 0.32 N and 0.49 N at 30 MPa of compression force, respectively (Figure 2). As compression force increasing, the difference of ejection force was increased a little, which means that the more amount of magnesium stearate was coated to the particles of the drug and to the other excipients. Thus, the friction energy of the coated

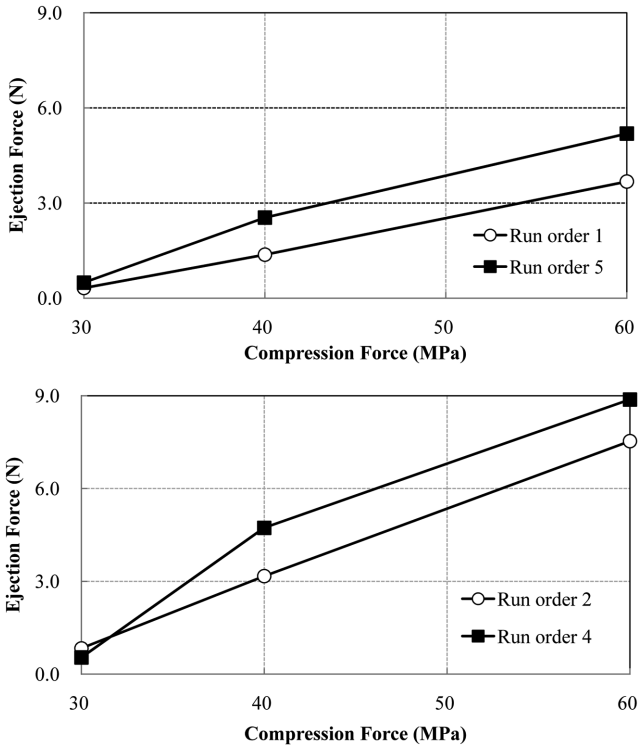

Figure 2. Effect of the amount of magnesium stearate on the experimental response, tablet ejection force. Run orders 1 & 5 and 2 & 4 had different amounts of magnesium stearate but the same mixing time.

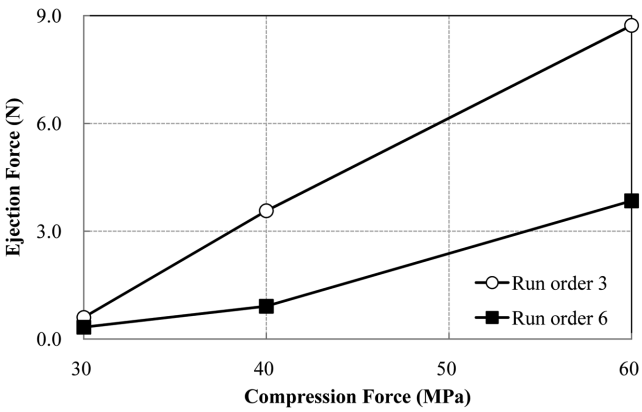

Figure 3. Effect of mixing time of magnesium stearate on the experimental response, tablet ejection force. Run order 3 & 6 had different mixing time but the amount of magnesium stearate was same.

powder was reduced between the die wall and the matrix tablet. However, longer mixing time may provide more energy which might result in shearing off of the lubricant particles. Therefore, the effect of the lubricant's amount may not that significant as observed in Run order 2 and 4.

The effect of mixing time at the experimental runs could be observed as to compare Run order 3 and 6 (Figure. 3). Run order 3 and 6 contained the same amount of magnesium stearate (1.50 w/w%) but different mixing time (Run order 3 of 2.76 min and Run order 6 of 11.24 min). The ejection force of Run order 3 and 6 was 0.60 N and 0.33 N at 30 MPa, respectively. The ejection force at 60 MPa of compression force was 8.73 N and 3.85 N, respectively. The difference of ejection forces was increased as the compression force increased. It means that the magnesium stearate coated the particles more efficiently as the mixing time increased. Hence, the coated powder reduced the friction energy between the die wall and the matrix tablet during the tablet ejection process.

Effects of magnesium stearate on the swelling properties of matrix tablets

In order to investigate the effects of various levels of magnesium stearate as well as its mixing time on the gelation of hydrophilic matrix tablets, the diameters of the gelated and non-gelated parts of the tablets were measured, and the gelation index was calculated using the equation (Table III). The gelation index is the percentage of the tablet that has undergone gelation after an immersion. Upon contact with the dissolution medium, the matrix tablet was hydrated and swelled causing a thick gel layer formation and expansion of the tablet's surface. However, the effective swelling was limited only to the horizontal side of the tablet due to the application of polyacrylate plates in this study.

The gelation study was carried out for 5 h with 4 replications in the experimental formulation. The 5 h time point might be sufficient to investigate the formulations since solid dosage forms usually stay in the upper GI (gastrointestinal) tract for about 5 h after administration, where the amount of GI fluid is sufficient to cause gelation (Davis et al., 1986). Gel thickness grew considerably moving inward as the hydration progressed, thus the dimensions of the solid core decreased. Because of the limited unidirectional contact of the dissolution medium, the gelation kinetics seemed to be very slow compared to those in previous studies (Sako et al., 1996; Conti et al., 2007). However, this method might be meaningful to differentiate various formulations and to select better ones.

Table III shows the mean and the variance of the experimental runs for the gelation study. The gelation at the end of 5 h ranged from 73.48 % (Run order 1 at 30 MPa) to 89.40% (Run order 3 at 40 MPa). The gelation properties at the end of study showed similar results regardless of the amount of magnesium stearate, its mixing time, and the compression force. The gelling process was fast upon contact with the dissolution medium (Figure. 4). However, after the fast initial gelation of 1~2 h, the later gelation kinetics was not rapid enough to gel completely. One reason for this is that the media penetration

Table III. *Experimental results for the gelation study based on the experimental runs with different compression force*

Compression Force (MPa)	Runs	0.5 h		1 h		1.5 h		2 h		2.5 h		3 h		4 h		5 h	
		$\bar{y}_1$	s_1^2	$\bar{y}_2$	s_2^2	$\bar{y}_3$	s_3^2	$\bar{y}_4$	s_4^2	$\bar{y}_5$	s_5^2	$\bar{y}_6$	s_6^2	$\bar{y}_7$	s_7^2	$\bar{y}_8$	s_8^2
30	1	19.78	0.45	35.47	0.45	56.96	0.23	62.02	0.63	63.45	0.21	64.96	0.49	68.90	0.92	73.48	0.57
	2	52.85	0.35	59.75	0.35	59.89	0.33	69.92	0.52	75.68	0.35	78.40	0.22	80.24	0.65	84.03	0.89
	3	30.29	1.00	46.69	1.00	52.39	0.23	55.52	0.40	63.19	0.46	69.36	0.69	77.49	0.62	81.96	0.54
	4	55.96	0.20	60.02	0.20	60.29	0.31	69.36	0.52	73.79	0.64	73.89	0.34	77.67	0.97	82.98	0.40
	5	23.39	1.26	47.67	1.26	53.00	1.40	60.56	0.24	68.33	0.40	71.90	0.75	79.72	1.03	85.18	0.48
	6	56.53	0.35	65.33	0.35	65.21	0.29	67.74	0.47	72.11	0.19	80.32	0.21	83.96	0.99	86.93	0.36
40	1	46.20	0.75	53.30	1.25	66.31	0.23	70.92	0.20	75.39	0.75	79.64	0.18	82.12	0.86	86.34	0.20
	2	40.02	0.63	56.68	0.86	63.32	1.40	71.68	0.37	77.49	0.70	80.82	0.31	81.80	0.43	86.07	0.50
	3	46.53	0.34	60.29	0.43	67.74	0.23	73.79	1.38	80.07	0.37	82.90	0.49	85.39	0.46	89.40	0.15
	4	36.76	0.59	52.39	0.46	60.83	0.31	65.70	0.42	69.81	0.47	73.89	0.88	79.72	0.45	85.39	0.66
	5	40.73	1.02	52.54	0.45	62.68	0.33	67.86	0.16	72.22	0.18	76.45	0.31	77.95	0.21	83.51	0.33
	6	40.02	0.53	52.24	0.21	60.56	0.29	67.74	0.84	73.17	0.56	75.88	0.55	78.58	1.25	83.36	0.59
60	1	40.91	0.57	54.79	1.25	66.43	0.40	75.88	0.63	77.95	0.20	79.72	0.42	83.89	0.49	87.12	0.92
	2	42.65	0.48	56.10	0.86	66.79	1.31	72.22	0.24	76.26	0.50	77.76	0.16	82.20	0.47	86.14	1.03
	3	45.87	0.54	55.08	0.43	68.33	0.15	71.79	0.40	73.79	0.15	78.58	0.84	84.25	0.18	87.44	0.62
	4	46.03	0.40	55.38	0.46	67.98	0.33	72.43	0.52	75.59	0.66	78.58	0.63	82.04	0.56	85.87	0.97
	5	41.43	0.89	53.90	0.45	63.19	1.50	70.92	0.52	74.29	0.33	76.83	0.24	82.75	0.20	87.06	0.65
	6	38.23	0.36	51.16	0.21	62.93	0.64	67.62	0.47	76.26	0.59	79.55	0.42	82.44	0.50	86.01	0.99

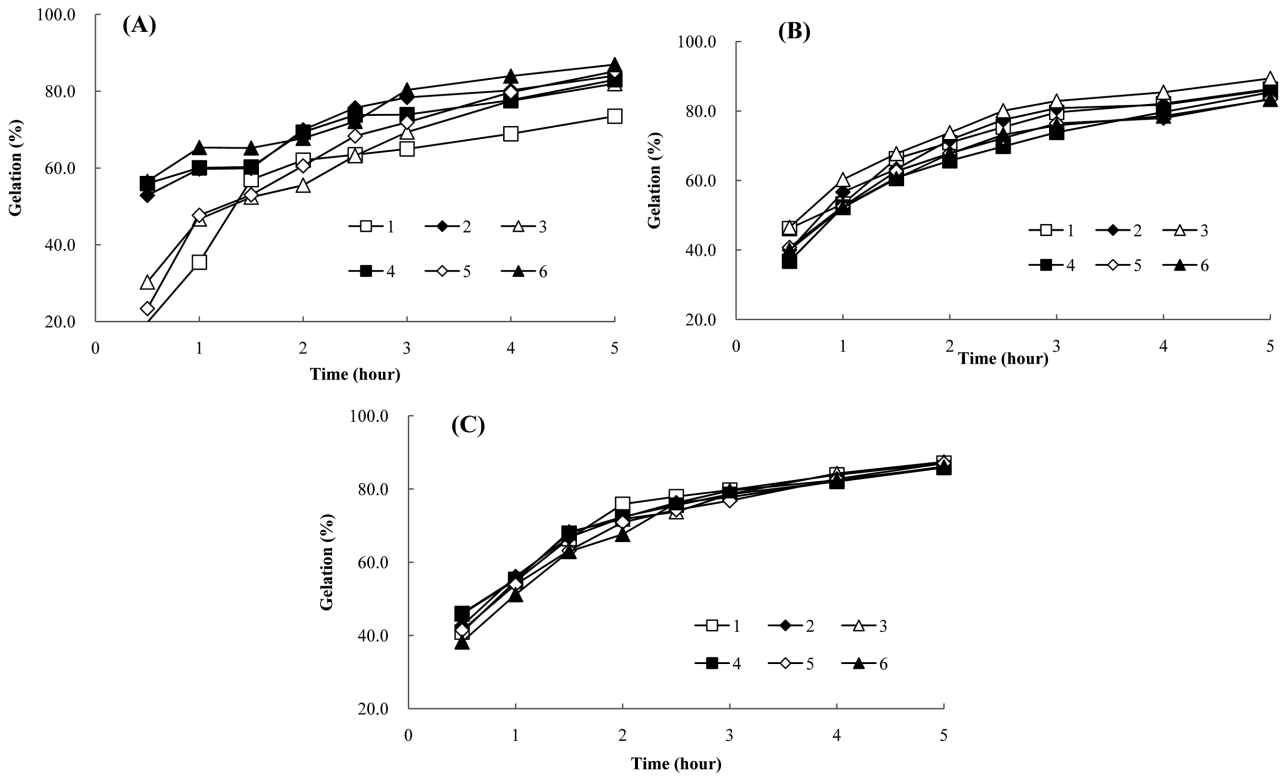

Figure 4. Swelling profiles (% gelation) of the matrix tablets under the different compression force with the experimental formats (n = 4): (A) compression force 30 MPa, (B) compression force 40 MPA, and (C) compression force 60 MPa.

rate was faster at the beginning since the fluid was in direct contact with the hydrophilic solid polymer. However, after a viscous gel layer had formed on the tablet surface, it could serve as a barrier to media penetration, decreasing the rate of diffusion of fluid into the matrix (Park et al., 2010).

At 30 MPa of the compression force, the effects of the amount of magnesium stearate and its mixing time on the matrix tablet were significant, especially for the initial stage (0.5~2h) (Figure. 4). For example, Run order 1 and 5 had the same mixing time of 7.00 min but the different amounts of magnesium stearate (2.20 and 0.79 w/w%, respectively). Gelation kinetics of Run order 5 at an early stage was faster than Run order 1. It means mixing time may affect the distribution of the lubricant, which can be a factor to be considered for the gelation.

As the compression force increased, the difference in the initial stage among the formulations was getting insignificantly smaller compared to the low compression force 30 MPa. Therefore, when to find an optimum formulation with decent tablet mechanical strength and swelling profiles, the amount of lubricant, mixing time, and compression force need to be considered together carefully. It has been considered that generally increasing the mixing time can have an effect on tablet mechanical strength. The longer the mixing continues, the more complete the coating of the adjacent particles will become, so decreases the force of inter-particle bonding. Therefore, longer mixing time with magnesium stearate gives an influence on decreasing the force of inter-particle bonding and this may affect the tablet's hardness and gelation kinetics.

Conclusions

With the various amount of magnesium stearate and mixing time, powder densities, tablet ejection force, and swelling properties of hydrophilic matrix tablets were evaluated and the results gave a rough guide how to choose suitable amount of the lubricant with optimum processing condition (mixing time) for the development of hydrophilic matrix tablet formulations. Moreover, when to find an optimum formulation with decent tablet properties, compression properties need to be considered together with the content of lubricants and their mixing time.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (20100002579).

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