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Improvement of the agitation granulation method to prepare granules containing a high content of a very hygroscopic drug

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Abstract

This study describes a new approach to the preparation of a granulate with a high content of a very hygroscopic powder or drug, using the agitation granulation method, and the development of a tablet formulation using these granulates. A Chinese medicine extract, Hatimi-zio-gan, was used as the model of a very hygroscopic drug. Among the several excipients tested, only porous calcium silicate could be used to prepare granules, with a mixing ratio (extract to porous calcium silicate) from 2:1 to 20:1. With other excipients, very large lumps were formed during the granulation process. The best mixing ratio of extract to porous calcium silicate was 6:1. For preparation of the granules, water could be added to the mixed powder within a range of 1- to 4-times the amount of porous calcium silicate. From these results, it was concluded that the ability of porous calcium silicate to hold large amounts of water in its numerous pores may allow for the preparation of granulates with a high content of very hygroscopic drugs. Starch with partial α-links, carboxymethyl starch sodium salt and crospovidone were used for selection of the disintegration agent. When crospovidone was used as a disintegration agent, tablets containing about 70% of the Chinese medicine extract disintegrated in less than 7 min, with good dissolution rates. The same process was applied to extracts of Hotyu-ekki-to, Syo-seiryu-to, Boi-ogi-to and Bohu-tusyo-san. The absorption of paeoniflorin, a characteristic monoterpene glucoside contained in Hatimi-zio-gan extract, was evaluated in beagle dogs after oral administration of the Hatimi-zio-gan tablets prepared in this study. The values of C_{max} and AUC obtained after administration of the tablets prepared in this study were significantly greater than those obtained for commercial tablets.

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Introduction

Among the various granulation methods for medicines are the dry process pulverization granulation method, the wet process extrusion granulation method, the fluidized bed granulation method, and the high-speed agitation granulation method. The fluidized bed granulation method and the high-speed agitation granulation method have been widely adopted in the pharmaceutical industry, as they use simpler processes and produce granulated products more efficiently than other methods (Japanese Pharmacopoeia, 14th edn).

In the wet granulation process, the method of addition, amounts of ingredients used, and time of addition of water or binder solution to the powder are very important factors. In general, water or binder solution is sprayed onto the powder to be granulated; the solution is added slowly in order to avoid rapid granulation. However, when a very hygroscopic powder is used, wet granulation is difficult because the powder rapidly absorbs water and becomes swollen or muddy.

Porous calcium silicate (Florite RE; FLR) possesses many interparticle (12 mm) and intraparticle (0.15 mm) pores on its surface (Yuasa et al 1996b). FLR has the ability to hold 4- to 5-times its own weight in liquid by virtue of its numerous pores. Takashima et al (1999) used FLR to prepare solid formulations of oily medicines. FLR is also used to improve drug solubility or the dissolution properties of tablets (Yuasa et al 1994, 1996a; Kinoshita et al 2002; Sharma et al 2005). These properties of FLR may result in its being applicable to wet granulation of very hygroscopic powders, because water retained by FLR is transferred to any hygroscopic material that is subsequently added to the vessel, leading

to granulation. However, there have been no reports of FLR being used to prepare granulates containing very hygroscopic powders with a view to tablet preparation.

Chinese medicines are very hygroscopic drugs. Granulates containing Chinese medicines can be prepared by wet or dry granulation methods at low drug contents, and tablets may be prepared from the granules. However, it is difficult to prepare granulates with high drug contents. The production of granulated products with a high content of Chinese medicine extract is desirable in order to produce solid tablets with a minimal amount of the required dose. The production of such a granulated product is an important development that could contribute towards easier dosing.

The purpose of this study was to develop a new agitation granulation method using FLR to produce a granulated product containing large amounts of a very hygroscopic drug such as a Chinese medicine extract, and to enable production of tablets with a high disintegration capability. We also evaluated the bioavailability of paeoniflorin, a characteristic monoterpene glucoside contained in Hatimi-zio-gan extract, after oral administration of the prepared tablets to beagle dogs.

Materials and Methods

Materials

Chinese medicine extracts Hatimi-zio-gan, Hotyu-ekki-to, Bohu-tusyo-san, Boi-ogi-to and Syo-seiryu-to (ALPS Pharmaceutical Ind. Co., Ltd) were used. FLR (Tokuyama Co., Ltd), magnesium stearate, light anhydrous silicic acid, hydrogen calcium phosphate, crystalline cellulose and synthetic aluminum silicate (Kyowa Chemical Industry Co., Ltd) were used as excipients. Partly pre-gelatinized starch, carboxymethyl starch sodium salt and crospovidone (BASF Japan, Ltd) were used as disintegrants, and magnesium stearate (Taihei Chemical Ind. Co., Ltd) was used as a lubricant. Kanebo Kampo Hatimi-zio-gan Ryo Extract Tablet S (400 mg tablets containing 200 mg extract; Kanebo Ltd, Tokyo, Japan) was purchased from a local drug store and used as the reference tablet.

Wet granulation

Water was added to FLR and mixed for 1 min at 200 rev min^{-1} using a blade and at 3000 rev min^{-1} using a cross-screw in a vertical granulator (FM-VG-05; Powrex Corporation). To this was added powdered Chinese medicine extract (dispersed in the water) and the mixture was stirred for 10 min at 200 rev min^{-1} with the blade and at 3000 rev min^{-1} with the cross-screw. The resulting granulate was dried in an oven (New HD-60; Nagano Scientific Equipment MFG Co., Ltd, Japan) at 70°C for 12 h.

Measurement of granular size

The diameters of the prepared granules were measured by an automatic granular size measurement apparatus (Robot shifter RPS-85C; Seishin Enterprise Co., Ltd, Japan) with seven attached sieves (1700, 1400, 1000, 850, 500, 355 and 75 μm).

Preparation of tablets

Before compression, the fixed-size granules (86.4%; Hatimi-zio-gan extract/FLR 6:1) were mixed with disintegrant (13.4%) and magnesium stearate (0.2%) at 25 rev min^{-1} for 10 min using a V-model mixer (S-5; Tsutsui Scientific Ind., Japan). The tablets were compressed using a rotary tableting machine (VIRG0812 SSS2AZ; Kikusui Seisakusho Ltd, Japan) with bi-convex punches 10 mm in diameter at a rotating speed of 25 rev min^{-1}. The compression pressure used during tableting was about 800 kg, and the weight of the resulting tablets was 400 mg containing 296 mg Hatimi-zio-gan extract.

Tablet hardness test

The hardness of the tablets was measured by diametral compression using a TM3-3 (Kikusui Seisakusho Ltd, Japan). Ten tablets were tested in each batch and the mean values were calculated.

Tablet disintegration test

Disintegration times were measured individually for six tablets in purified water at 37 ± 0.5°C using a JP XIV apparatus (NT-2HS; Toyama Sangyo Co., Ltd, Japan) and the mean values were calculated.

Tablet dissolution test

Dissolution tests were performed using a JP XIV apparatus (NTR-6100; Toyama Sangyo Co., Ltd, Japan). One tablet containing Hatimi-zio-gan extract was placed in the dissolution medium (900 mL of purified water) at 37 ± 0.5°C, and the paddle was rotated at 100 rev min^{-1}. The amount of dissolved paeoniflorin, a characteristic monoterpene glucoside contained in Hatimi-zio-gan extract, was determined using high-performance liquid chromatography (HPLC). Six tablets were tested and the mean values were calculated.

Administration of Hatimi-zio-gan tablets to beagle dogs

Four adult male beagle dogs, 10–13 kg, were used in accordance with the Guidelines for Animal Experimentation of Mukogawa Women's University, which are based on the Guidelines for Animal Experimentation of the Japanese Association for Laboratory Animal Science. The dogs were fasted overnight for at least 12 h with free access to water. Fifteen of the tablets prepared in this study, or 22 reference tablets (containing the same dose of Hatimi-zio-gan extract), were administered with water in a crossover manner, with a 1-week wash-out period. The tablets were administered with about 10 mL of water for every five tablets, and the total volume of water administered was unified to 40 mL. Blood samples (2.5 mL) were taken 30 min before and 0.5, 1, 2, 4, 6 and 8 h after administration. Serum was

separated by centrifugation at 2000 *g* for 10 min and stored at −20°C until analysis. Water was given ad libitum but no food was given during the study.

The maximum serum concentration of paeoniflorin (C_{max}) was determined from the individual serum concentration–time profiles. The area under the serum paeoniflorin concentration versus time curve (AUC) was calculated by the trapezoidal method from zero to the final sampling time.

Analytical method for paeoniflorin

Concentrations of paeoniflorin in the dissolution medium were determined by HPLC (Shimadzu LC-10A liquid chromatograph), using a variable wavelength UV-vis detector (SPD-10vp) set at 280 nm. The analytical column was TSK-gel ODS-80TSQ. The mobile phase consisted of water, acetonitrile and phosphoric acid (850:150:0.8) and the flow rate was 1 mL min^{-1}. A, 20-mL sample of the dissolution medium was injected into the HPLC system. Concentrations of paeoniflorin in dog serum were determined according to the enzyme immunoassay method of Takeda et al (1995).

Statistical analysis

All results were expressed as mean ± s.e. Statistical significance was determined by analysis of variance with the Bonferroni method used to compare individual data for a significant *F* value. Differences were considered significant when the calculated *P* value was < 0.05.

Results and Discussion

Preparation of granules via the wet granulation method

It is very difficult to prepare granules containing a high content of a very hygroscopic drug using the wet granulation method because the drug rapidly absorbs water and becomes swollen or muddy. To resolve this problem, FLR was selected as an excipient. FLR has good shaping properties due to its large, porous and petaloid structure and its ability to absorb 4- to 5-times its own weight in liquid (Aili et al 1992). Granulation was carried out as described above using a high speed agitation granulating machine. Hatimi-zio-gan was used as a model medicine. First, FLR and water were added to the vessel of the granulating machine and stirred; after sufficient dispersion of water into the FLR, Hatimi-zio-gan extract was added. Water was not added during the course of the granulation. The progress of granulation was found to be controllable by the amount of water retained in the FLR and the speed of the blade. When water was added directly or by spraying onto the mixture of FLR and Hatimi-zio-gan extract, large lumps were formed. Dependence on this method, which is different from conventional methods involving the gradual addition of water or spraying, prevented rapid progress of granulation.

Five other excipients (calcium stearate, light anhydrous silicic acid, hydrogen potassium phosphate, crystalline cellulose and synthetic aluminum silicate) were also used in the wet granulation method. However, with all of these, large lumps of extract powder formed during the granulation process, and granulates were not obtained. Chinese medicine extracts are very hygroscopic and become lumpy when they absorb moisture. It was not clear why the granulation process was successful with FLR, but it may be attributed to the greater ability of FLR to absorb liquids compared with the other excipients. It may be concluded that water contained in the nano-sized pores of FLR moved into the Hatimi-zio-gan extract very slowly. Further studies are necessary to elucidate the mechanism of this process. In addition, no binders were used in this study; the soluble starch and polysaccharides contained in the extract powder may have acted as a binder.

To determine a suitable ratio of extract to FLR in the granulate, eight formulations were compared (Table 1), with the ratio of extract to FLR varying from 20:1 to 2:1, and the ratio of FLR to water remaining constant at 1:1.8. Table 2 shows the mean granule diameter (D50) after granulation with a vertical granulator. In formulations 1 and 2, large lumps of the extract were formed, and granulates were not obtained. In formulations 3–7, the granulation process succeeded without the formation of lumps. Progress of the granulation was suppressed to varying extents depending upon the amount of FLR. In particular, in formulation 6, the extract to FLR ratio of which was 6:1, the granulation process continued for more than 15 min without any lumps.

Next, we investigated the effect of water content on the granulation process. Water was added to the mixed powders (Table 1, formulation 6) in an amount between 1- and 4-times that of FLR. The values of D50 increased as the amount of water increased to 4-times that of FLR (Table 3). However, when more than this was added, the powders in the vessel formed large lumps and granulates were not obtained. This may be due to water having sunk into the extract powders in amounts beyond the capacity of FLR.

Selection of disintegrant

To select a suitable disintegrant for this study, partly pre-gelatinized starch, carboxymethyl starch sodium salt and crospovidone were used. Tablets were prepared by the fixed-size

Table 1 Formulation of granules and amounts of added water

	Formulation							
	1	2	3	4	5	6	7	8
Hatimi-zio-gan extract	400.0	380.0	380.0	350.0	350.0	350.0	350.0	280.0
FLR (g)	20.0	38.0	42.2	43.8	50.0	58.3	87.5	140.0
Purified water (g)	36.0	68.4	76.0	78.8	90.0	104.9	157.5	252.0

Table 2 Mean granule diameter (D50) after granulation

	Formulation			
	3	4	5	6
D50 (μm)	1397 ± 151	1069 ± 70	1095 ± 51	856 ± 8*

Each value is the mean ± s.e., n = 3. Formulations 3, 4, 5 and 6 correspond to those shown in Table 1. *$P < 0.05$, significantly different compared with Formulation 3.

Table 3 Effect of added water amount on mean granule diameter (D50)

	Ratio			
	1.0	1.8	2.3	4.0
D50 (μm)	332 ± 4	856 ± 8*	1154 ± 86*	1398 ± 127*

Each value is the mean ± s.e., n = 3. The ratio values represent the ratio of water to FLR (w/w). *$P < 0.05$, significantly different compared with the 1.0 ratio.

granules (86.4%; formulation 6 in Table 1), disintegrant (13.4%) and magnesium stearate (0.2%). Although all tablets had hardness values of more than 5 kgf, the disintegration times were different depending on the disintegrant; crospovidone proved to be the best disintegrant in this system (Table 4). However, when the tablets were made by direct stressed compression of a mixture of these disintegration agents and the mixed powder, the disintegration time was more than 50 min, and significant differences in disintegration time were not observed. It is known that the mechanism of disintegration differs depending on the structure of the disintegration agent. The mechanism of disintegration by the starch family is based on swelling, whereas that of crospovidone is thought to be rapid penetration of water due to high capillary activity (Kanig & Rudnic 1984; Visavarungroj & Remon 1990). From these results, it was concluded that rapid penetration of water into the granules plays a very important role in the disintegration process in this system.

When compared with Hatimi-zio-gan tablets on the market, tablets containing crospovidone had a disintegration rate of less than half of that of reference tablets (Table 4), and it was clear that tablets containing crospovidone showed good disintegration properties. Therefore, crospovidone was used as a disintegrant in the preparation of tablets.

In-vitro dissolution test

The results of dissolution studies of paeoniflorin, a characteristic monoterpene glucoside contained in Hatimi-zio-gan extract, using the tablets prepared in this study and reference tablets are shown in Figure 1. The dissolution rate of paeoniflorin from the tablets prepared in this study was greater than that of the commercial tablets. The time taken for 50% dissolution, T50%, was 3 min for the tablets prepared in this study and 15 min for reference tablets. For the tablets prepared in this study, complete dissolution was achieved within 10 min. The mean dissolution time of paeoniflorin was 20 min for the tablets prepared in this study and 60 min for reference tablets. These results confirm the fast dissolution of paeoniflorin from the tablets prepared in this study.

Pharmacokinetic study

To further investigate the properties of the tablets prepared in this study, pharmacokinetic studies were carried out on beagle dogs. Fifteen tablets prepared in this study or 22 commercially available tablets (containing the same dose of Hatimi-zio-gan extract) were administered with 40 mL of water. Profiles of serum concentrations of paeoniflorin versus time are shown in Figure 2, and the calculated pharmacokinetic parameter values are shown in Table 5. Although there was no significant difference in T_{max} between the tablets prepared in this study and the reference tablets, C_{max} and AUC were significantly increased in the tablets prepared in this study. The high absorption of paeoniflorin from the tablets prepared in this study may be due to rapid disintegration of the tablet (Table 4) and fast dissolution of paeoniflorin in the intestinal fluid.

Tablets of various Chinese medicine extract powders

The application of this method to other Chinese medicine extracts (Bohu-tusyo-san, Boi-ogi-to, Syo-seiryu-to and Hotyu-ekki-to) was also investigated. The same formulation as formulation 6 in Table 1 was used for all extract powders. All of the extract powders could be granulated, and tablets were made under the same conditions as those of Hatimi-zio-gan. The mean disintegration times of Bohu-tusyo-san, Boi-ogi-to, Syo-seiryu-to and Hotyu-ekki-to tablets were 7.8, 7.6, 7.0 and 7.8 min, respectively. From these results, it was concluded that the wet granulation procedure in this study is applicable to various Chinese medicine extract powders.

Table 4 Effect of disintegrant on the disintegration time of Hatimi-zio-gan tablets

	Partly pre-gelatinized starch	Carboxymethyl starch sodium	Crospovidone	Reference tablet
Disintegration time (min)	19.9 ± 2.1*	17.3 ± 2.0*	5.9 ± 0.1	18.5 ± 0.4*

Each value is the mean ± s.e., n = 6. *$P < 0.05$, significantly different compared with crospovidone.

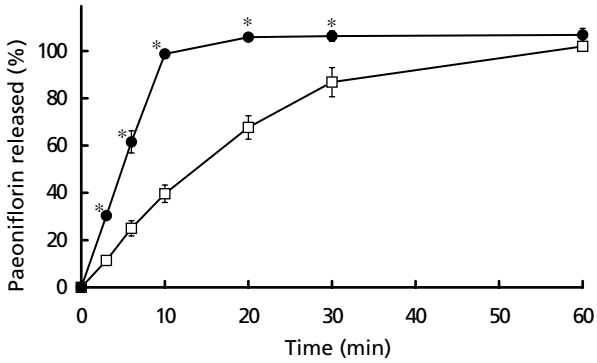

Figure 1 Dissolution profiles of paeoniflorin from Hatimi-zio-gan tablets made in this study (●) and from reference tablets (□). Each point is the mean ± s.e. of six experiments. $*P < 0.05$, significantly different compared with the reference tablets.

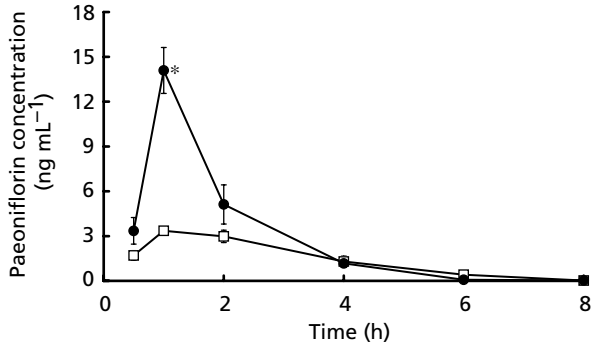

Figure 2 Profiles of plasma paeoniflorin concentration versus time after oral administration of Hatimi-zio-gan tablets tablets made in this study (●) and of reference tablets (□) to beagle dogs. Each point shows the mean ± s.e. for four dogs. $*P < 0.05$, significantly different compared with the reference tablets.

Table 5 Pharmacokinetic parameters of paeoniflorin after oral administration of Hatimi-zio-gan tablets to dogs

	C_{max} (h)	AUC (ng h mL^{-1})
Tablets prepared in this study	14.1 ± 1.5*	23.1 ± 3.4*
Reference tablets	3.4 ± 0.2	11.3 ± 1.8

Each value is the mean ± s.e. of four dogs. $*P < 0.05$, significantly different compared with the reference tablets.

Conclusion

It was found that by performing a new wet granulation process based on the retention of water by FLR, typical hygroscopic drugs such as Chinese medicine extracts could be granulated. In tablets formed by compression of these granules, a disintegration agent was found to function effectively, even if the tablet contained a high concentration of Chinese medicine extract. It was also found that in order to obtain proper granules, the mixing ratio of Chinese medicine extract, FLR and water may be optimized. To obtain tablets with good disintegration properties, it was found that crospovidone was the most effective disintegrant. The resulting tablets contain about 70% Chinese medicine extract, and have a hardness value of greater than 5 kgf and a disintegration time of less than 10 min. Furthermore, they displayed fast dissolution and superior bioavailability in beagle dogs compared with commercially available tablets. Further investigation of the application of this process to hygroscopic drugs other than Chinese medicine extracts and the detailed disintegration mechanism of the tablets obtained by this procedure is appropriate.

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